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ANGIOGRAPHY IN CARCINOMA OF THE RENAL PELVIS

by

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Renal angiography has during the last decade constituted a routine diagnostic procedure affording invaluable information on various conditions of disease. Furthermore, accumulated experiences of the method have considerably increased our knowledge of the normal and pathologic roentgen appearances of the renal vascular system.

The great value of renal angiography in tumors invading the renal parenchyma is indisputable. It is generally held, however, that carcinoma of the renal pelvis is avascular and never produces characteristic angiographic appearances (NELSON 1942, DOSS 1946, SHAPIRO 1953, CREEVY & PRICE 1955, RICHES 1955, 1959, EDSMAN 1957, EVANS 1957). If the tumor is located in the intrarenal part of the pelvis and infiltrates the parenchyma the vessels within the infiltrated region have a reduced caliber and are displaced, and an irregular defect is produced in the nephrographic phase (DOSS, EDSMAN); tumor vessels have been observed in a few cases of infiltrating renal pelvic carcinoma (PIRONTI & TARQUINI 1958, GREGG 1958, VOGLER & HERBST 1958).

If the tumor lies in the confluent part of the renal pelvis, the angiographic appearances may be the same as in advanced hydronephrosis viz. indicate a markedly reduced blood supply and displaced vessels (RUNSTRÖM 1948, PALLÖV 1952, WEYDE 1952, MORINO & TARQUINI 1957, EDSMAN, PIRONTI &

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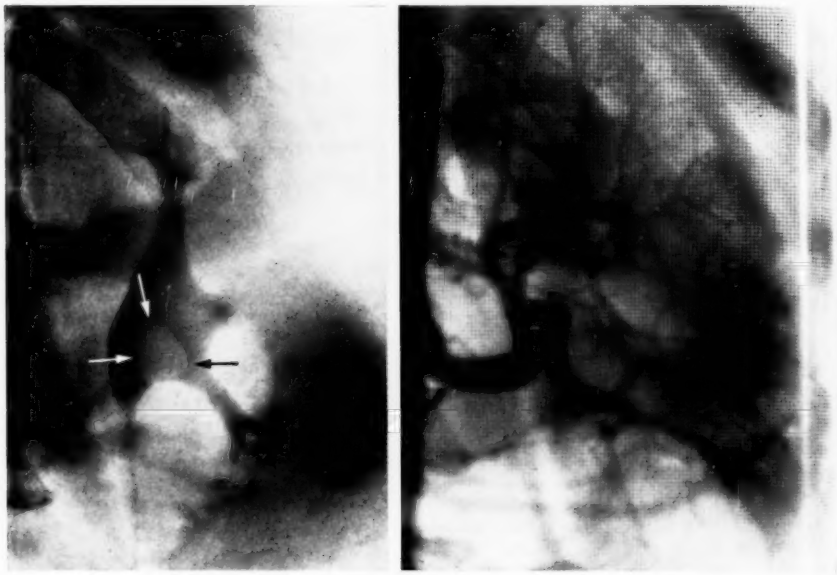

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Fig. 1. Case 1. Papillary carcinoma of left renal pelvis. a) Urography: small tumor in lower part of pelvis. b) Aortic renal angiography: normal findings.

TARQUINI inter al.). A 'silent' kidney may be found at urography and the tumor of the kidney pelvis revealed at pyelography; these methods have thus been considered those of choice in the diagnosis of renal pelvic tumors (CREEVY & PRICE, PLOTEGHER 1957, inter al.).

The angiographic appearances of the vessels supplying the renal pelvis and upper ureter have been previously described (BOIJSEN 1959). Normally these vessels are too minute to be visible during angiography. In two of three cases of renal pelvic carcinoma pathologic vessels arising from a displaced and widened pelvoureteric artery could however be seen at selective renal angiography. Our own experiences of the angiographic characteristics of renal pelvic tumors are now reported.

Material. Ten cases of unilateral renal pelvic tumors were examined by renal angiography. Of these, 8 were proved histologically after nephrectomy (7) or autopsy (1). Two cases were not subjected to operation and therefore not verified, but both had histologically proved carcinomas of the bladder and these were presumed to represent metastases from angiographically malignant tumors of the kidneys. Two of the histologically proved renal pelvic tumors were

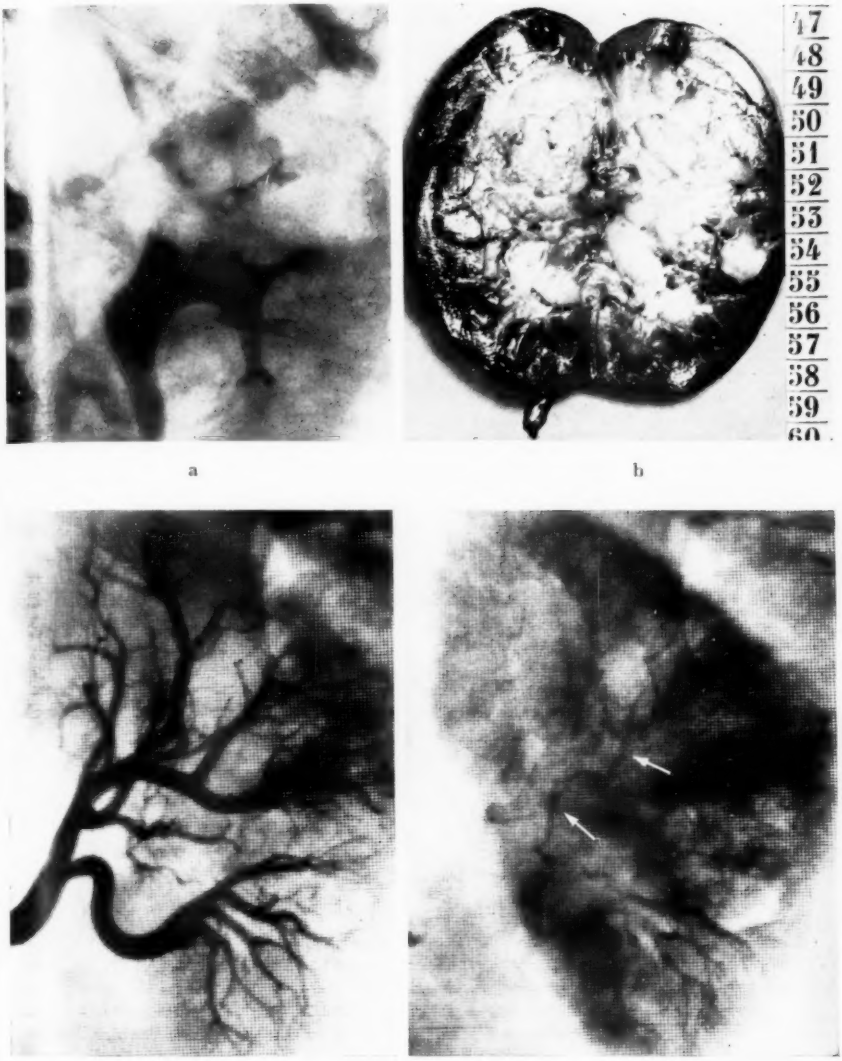

Fig. Case 2. Papillary carcinoma of left renal pelvis. a) Urography: upper ramus of pelvis distended but not obstructed by tumor. b) Operation specimen, small tumor in upper part of renal sinus, normal parenchyma. c) and d) Selective renal angiography: normal vascularization of renal parenchyma. Late in the arterial phase (d) a wide and tortuous pelvic artery (→) supplies the tumor.

combined with bladder growths and two with ureteric tumors, all of the same type as in the renal pelvis. The ages of the patients ranged from 44 to 73 years.

It is possible from a roentgendiagnostic and especially from an angiographic point of view to divide the present collection of renal pelvic tumors into three groups. The *first* group is represented by a small renal pelvic tumor in a normally functioning kidney; in the *second* group the renal pelvic tumor infiltrates the renal parenchyma; and the *third* group is characterized by a renal pelvic tumor obstructing the urinary outflow and causing complete or localized hydronephrosis.

Case reports

Cases belonging to group I

Case 1. Male, aged 60, with intermittent haematuria for six months. *Urography:* Tumor, cm in diameter, at base of left renal pelvis. *Aortic renal angiography:* Normal left renal artery and branches; normal accumulation of contrast medium in renal parenchyma. *Cystoscopy:* Tumor on right side of bladder. *Operation:* Resection of the tumors of left renal pelvis and bladder. *Pathology* report: Both tumors differentiated papillary carcinomas: no infiltration.

Case 2. Male, aged 64, with abdominal pain for a week and haematuria (microscopy). *Urography:* A 2 by 3 cm irregular tumor in upper part of left renal pelvis. *Selective left renal angiography:* Renal artery and branches not displaced. A tortuous, irregular artery branching from the dorsal artery supplied the tumor. Normal accumulation of contrast medium in renal parenchyma. *Operation:* Ureteronephrectomy. *Pathology* report: Large differentiated papillary tumor distending upper part of renal pelvis. No infiltration of renal parenchyma.

Comments

Small kidney pelvic tumors in a normally functioning kidney may easily be diagnosed by urography. As long as the growth is small, is confined to the intrarenal part of the pelvis, and does not infiltrate the parenchyma, it is supplied by the small renal pelvic vessels that arise from the primary branches of the renal artery. These fine vessels are increased in width when supplying a tumor but are, in our experience, too small to be seen at aortic renal angiography (Case 1). Selective renal angiography may, however, because of the higher density of the contrast medium, show a widened, tortuous renal pelvic artery supplying the tumor (Case 2). Irrespective of which type of angiography is chosen no tumor vessels will be demonstrated as long as the renal parenchyma is intact.

Cases belonging to group II

Case 3. Female, aged 73, with a four-year history of right loin pain and haematuria. *Urography:* Upper part of right kidney widened with no excretion evident in this region; the remainder of the kidney functioned normally. Ramus of upper calyx abruptly cut off. *Aortic renal angiography:* The right renal artery was slightly reduced in width. The intrarenal branches in the upper half of the kidney were slightly narrowed, somewhat sparse, but not displaced. A tortuous vessel running inwards and downwards represented a widened pelvo-ureteric artery. No tumor vessels present but in the upper half of the kidney the contrast medium accumulated irregularly with no demarcation between the cortex and the medulla as in the lower half. Patient was not operated upon and died 9 months later. *Postmortem examination:* Anaplastic solid carcinoma arising from upper part of right renal pelvis, infiltrating the parenchyma, and extending distally around the lower part of the renal pelvis and upper part of the ureter. Metastases in the abdomen and lungs.

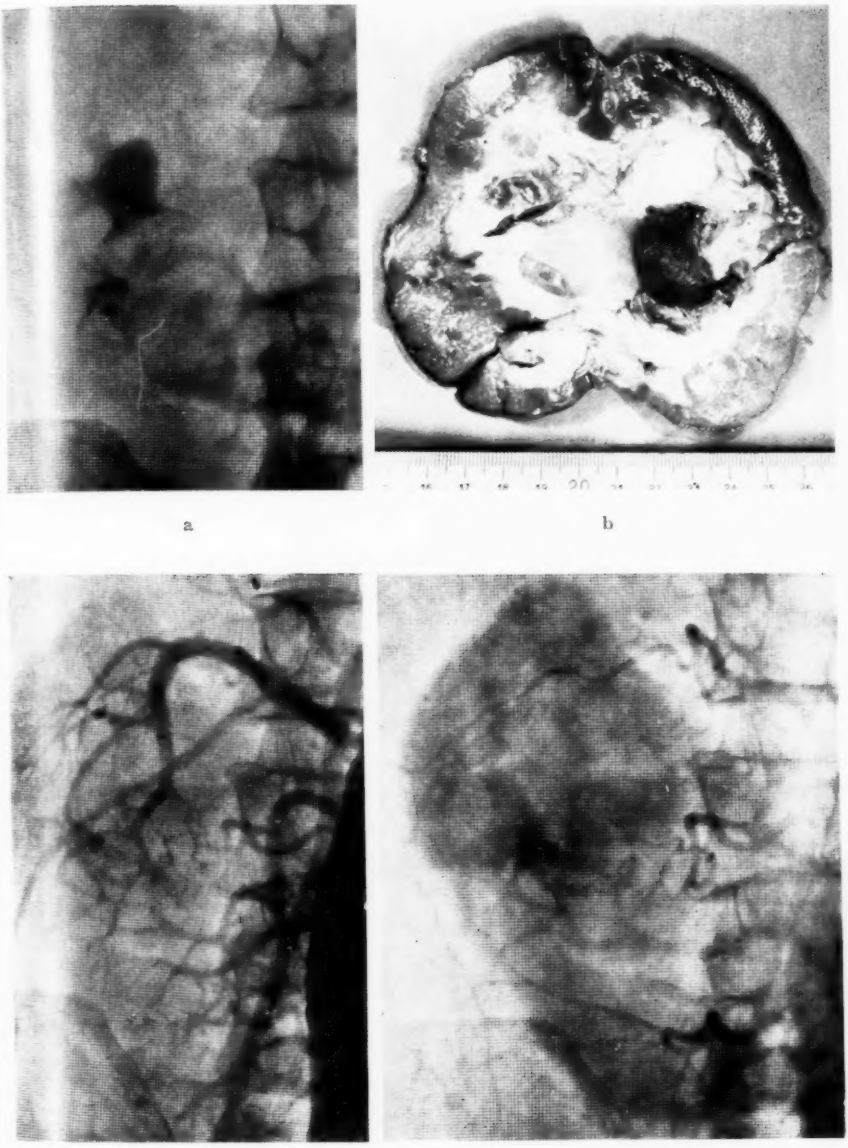

Fig. Case 4. Papillary carcinoma of right renal pelvis infiltrating parenchyma. a) Urography: tumor bulging into right pelvis of a horseshoe kidney, no obstruction to urinary outflow. b) Operation specimen. c) and d) Aortic renal angiography: tumor vessels arising from peripheral branches of main renal artery supply the tumor.

Case 4. Male, aged 61, with right loin pain and intermittent haematuria for one month. *Urography:* Horse-shoe kidney with irregular calcifications in the central part of the right lobe; medial to the calcifications a tumor, 3 × 4 cm in size, bulged into the confluent part of the renal pelvis. *Aortic renal angiography:* Right kidney supplied by two vessels of normal width; irregular vessels as well as accumulation of contrast medium evident within the tumor shown at urography. *Operation:* Nephrectomy. *Pathology* report: Differentiated papillary pelvic tumor, about the size of a walnut, arising from a middle calyx and bulging into the renal pelvis. Renal parenchyma infiltrated at the base of tumor.

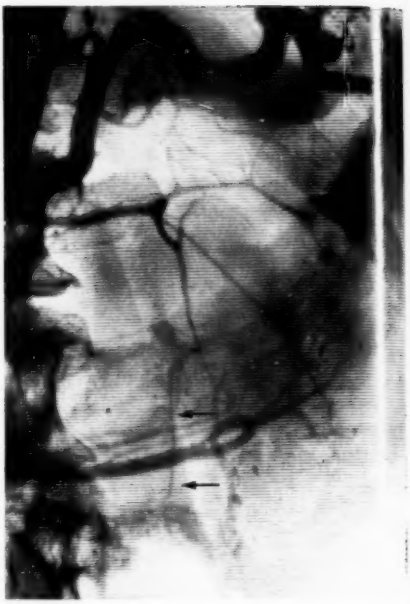

Fig. 4. Case 5. Papillary carcinoma of left renal pelvis and upper ureter. Aortic renal angiography: renal artery and branches small and displaced, widened ureteropelvic artery (→) arising from dorsal artery supplying the tumor with pathologic vessels. No accumulation of medium in parenchyma.

Comments

If the tumor arises in the intrarenal part of the renal pelvis and infiltrates the parenchyma a primary carcinoma of the latter cannot be excluded, as urography, pyelography, as well as angiography, may produce the same appearances in both types of carcinoma. When a renal pelvic carcinoma grows into the parenchyma the infiltrating part of the tumor is supplied by the peripheral branches of the renal artery. If a renal carcinoma bulges or infiltrates into the kidney pelvis this part of the tumor is supplied by the more centrally placed, fine renal pelvic vessels. If no tumor vessels are evident in an infiltrating renal pelvic carcinoma, there will be an irregular accumulation of medium within the infiltrated region and no demarcation between the cortex and the medulla, just as in a renal carcinoma.

Cases belonging to group III

Case 5. Male, aged 59, with loss of weight and lassitude for six months. *Urography:* Enlarged kidney with irregular surface; no evidence of excretion. *Aortic renal angiography:* Narrowed left renal artery with very small and displaced branches. The ureteropelvic artery arose from the distal branch of the dorsal artery, turned inwards and downwards, and was wider than the parent branch; small tumor vessels were evident in the region it supplied. *Operation:* Ureteronephrectomy. *Pathology* report: Differentiated papillary tumor at ureteropelvic junction with small growths in upper part of ureter. No infiltration into parenchyma.

Case 6. Female, aged 56, with haematuria for three weeks. *Urography:* Somewhat enlarged nonfunctioning left kidney with irregular surface. *Aortic renal angiography:* Markedly narrowed left renal artery with branches, and the intrarenal branches displaced and giving rise centrally to pathologic vessels. A wide ureteropelvic artery from the dorsal artery supplied a tumor with pathologic vessels. *Pyelography:* Irregular tumor within renal pelvis and upper ureter; marked peripheral hydronephrosis. *Operation:* Ureteronephrectomy. *Pathology* report: Peripheral

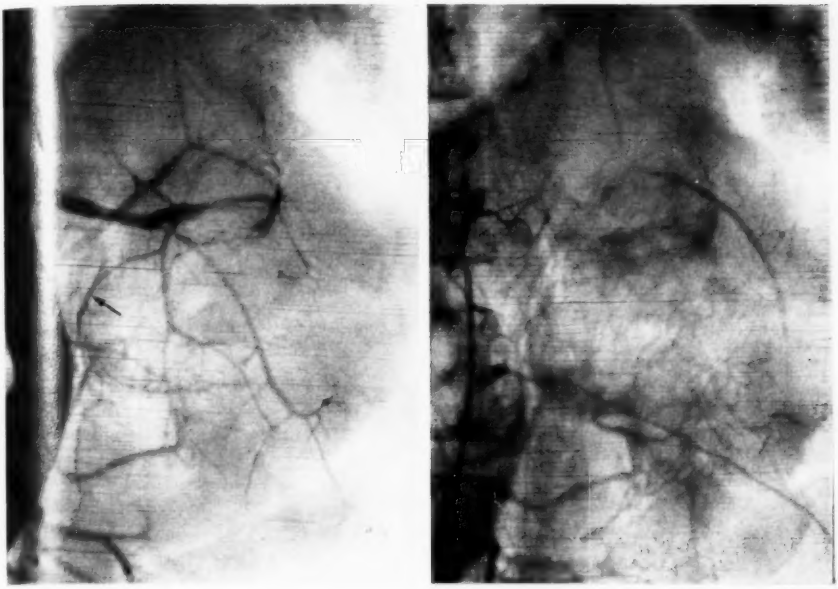

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Fig. 5. Case 6. Papillary carcinoma of left renal pelvis and ureter.

a) and b) Aortic renal angiography: reduced blood supply to enlarged left kidney with irregular lateral contour; widened ureteropelvic artery (→) can be followed distally and pathologic vessels are seen within its region of supply. Tumor vessels arising from the widened pelvic vessels are also evident in the central part of the kidney.

c) Arteriography of operation specimen showing same appearances. Ureteropelvic artery widened down to the site of the tumor in the ureter.

a b

Fig. 6. Case 7. Papillary carcinoma of right renal pelvis. a) and b) Selective renal angiography: enlarged kidney, narrowed renal artery and branches displaced by large tumor. A middle capsular artery (←) is displaced by the tumor. A widened and displaced ureteropelvic artery (←) supplies the tumor with pathologic vessels, and widened pelvic arteries supply the intrarenal part of the tumor.

hydronephrosis with much reduced parenchyma. Advanced papillomatous changes in upper part of ureter and central part of renal pelvis. Poorly differentiated papillary carcinoma, rich in vessels.

Case 7. Male, aged 44, with intermittent haematuria and right loin pain for two years. *Cystoscopy:* Two large papillomatous tumors in bladder. *Urography:* Non functioning, enlarged right kidney with irregular lateral surface. *Pyelography:* Confluent part of the right renal pelvis deformed by a tumor. Normal ureter. *Selective renal angiography:* Right renal artery and its branches narrowed and markedly displaced. Pathologic vessels evident centrally in the enlarged kidney and arising medial to the kidney from widened ureteropelvic artery; a capsular artery was greatly displaced by the tumor. No accumulation of medium within the renal parenchyma. *Operation:* Ureteronephrectomy and removal of bladder growths. *Pathology report:* Differentiated papillary tumor, about 10 × 5 cm in size, in right renal pelvis; gross hydronephrosis. Renal parenchyma reduced to a thin layer. Infiltration of tumor into surrounding fatty tissues and into lymphatics. Vesical tumors of the same histologic type as renal pelvic tumor.

Case 8. Male, aged 61, with left colicky pain for four months and slight haematuria for one month. *Urography:* Large tumor in upper part of left kidney obliterating upper calyces and displacing remainder of renal pelvis downwards. *Aortic renal angiography:* An artery of no mal

cali r supplied the lower pole, and a narrowed artery the remainder of the kidney; the intra-ren branches of the latter were narrowed and displaced. A large number of small tumor vess were evident in the upper half of the kidney late in the arterial phase. Normal accum ation of contrast medium in lower pole with differentiation between the cortex and the med la; practically no medium evident in remainder of kidney. *Operation:* Nephrectomy. The idney appeared normal apart from slight enlargement of its upper pole. Ureterectomy not rformed as there was no macroscopic evidence of renal pelvic carcinoma. *Pathology* repo : Differentiated papillary tumor at upper part of renal pelvis displacing and reducing the renchyma to a thin layer. No infiltration into parenchyma.

Com nts

A of the proved cases of tumor at the ureteropelvic junction had a urographically 'silent' kidn , which was enlarged and had an irregular surface. Thus urography cannot give a defi e diagnosis of renal pelvic carcinoma. Only in one of the cases was it possible to demonstrat a papillary tumor by pyelography.

R nal angiography, on the other hand, in all three cases produced conclusive evidence of a renal growth causing obstruction. The signs were as follows: (1) A markedly reduced vascular supply to an enlarged kidney and displacement of the central branches of the renal artery by the tumor in the confluent part of the renal pelvis. (2) A wide ureteropelvic artery supplying the tumor with pathologic vessels medial to the kidney. (3) Because of the reduced parenchyma and the growth of the tumor, practically no contrast medium accumulated in the nephrographic phase. (4) Due to the advanced atrophy of the renal parenchyma, tumor vessels arising from widened pelvic arteries were evident late in the arterial phase within the intrarenal part of the renal pelvis.

If the renal pelvic carcinoma arises within a ramus of the renal pelvis and causes a localized pressure atrophy of the parenchyma the angiographic appearances will be similar but confined to only a part of the kidney (Case 8). A widened ureteropelvic artery will not be apparent because the tumor is not within its field of supply.

Discussion

Three types of renal pelvic carcinoma could be differentiated in the present investigation.

Small tumors of the renal pelvis which do not infiltrate the renal parenchyma (group I), may be demonstrated at urography but for the final diagnosis renal angiography may provide supplementary information of great value. No tumor vessels, or accumulation of contrast medium within the tumor, will be evident, as in the first place the tumor vessels in a renal pelvic carcinoma are narrow and sparse and secondly, the accumulation of medium in the unaffected renal parenchyma will hide these fine vessels.

Infiltrating carcinoma of the renal pelvis (group II) cannot be differentiated from renal carcinoma of low vascularization either by urography or renal angiography. Three tumors were of the infiltrating type in the present material. One of these was not verified (Case 9), but at cystoscopy a biopsy was made of a large bladder growth, which histologically had the characteristics of a vesical carcinoma, and a malignant tumor in the right kidney was demonstrated by renal angiography. Thus, in all three cases a diagnosis of carcinoma was

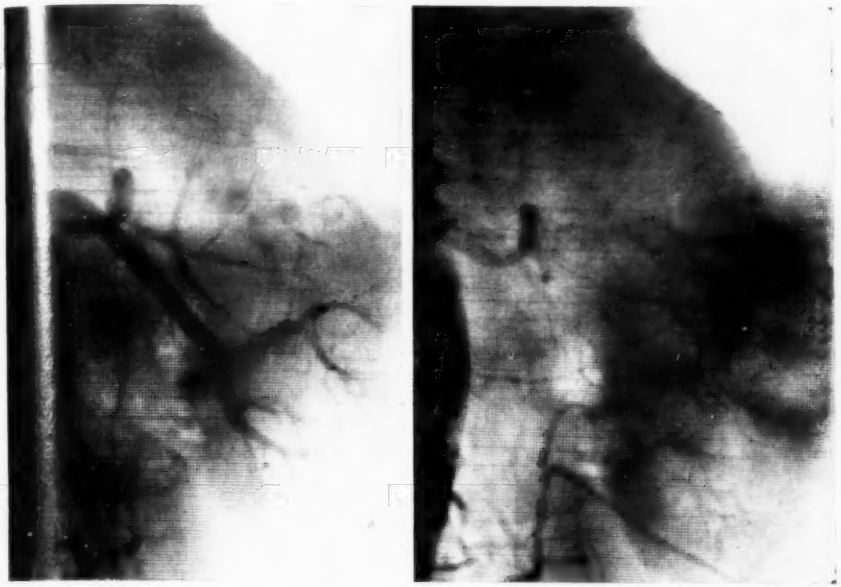
made although it was not possible to state that the tumor arose from the re al pelvis. Two of the cases had tumor vessels arising from the peripheral branc es of the renal artery and a wide ureteropelvic artery supplied the tumor; thou gh rare, a renal carcinoma may in fact be supplied by a ureteropelvic art ry (BOIJSEN). If, on the other hand, the tumor arises from the upper part of he ureter or from the extrarenal part of the renal pelvis it is always supplied by the ureteropelvic artery, which will be filled at renal angiography. Of the 10 cases of renal pelvic tumors a wide ureteropelvic artery was evident in 6, t at is in all cases in which the tumor arose or extended medial to the kidney.

From a surgical point of view the diagnosis of renal pelvic carcinoma is i n-portant because ureteronephrectomy should then be performed. If the di g-nosis is not clear preoperatively it is usually impossible to decide the tu or type during the operation (O'CONOR 1956, TAYLOR 1959, inter al.), and he ureter will not be removed, with all the attendant risks. This is especially t ue when the tumor causes hydronephrosis, i.e. is of the same type that is diffi lt or impossible to diagnose by urography or pyelography.

Contrary to previous conceptions renal angiography offers the most im-portant contribution to the diagnosis when the renal pelvic growth obstructs the urinary outflow (group III), and it is furthermore safe and conclusive. In 5 of the 10 cases there was a total (4) or a local (1) hydronephrosis with re-sultant advanced pressure atrophy and in only one of these was it possible by means of urography or pyelography to establish a correct diagnosis. One case was not histologically proved (Case 10), but the patient had a verified vesical carcinoma and the angiographic characteristics were the same as in the proved tumor cases causing hydronephrosis.

Previous authors have stated that hydronephrosis caused by a tumor of the renal pelvis cannot be distinguished from other types of hydronephrosis unless tumor vessels are shown. Such vessels may, according to these authors, be demonstrated only in a few cases and then only when there is infiltration of the parenchyma. In the present material, however, tumor vessels were ob-served in all cases in which a reduction of the parenchyma due to pressure atrophy was present. The pathologic vessels are always small and sparse, and arterio-venous shunts, so often seen in renal carcinoma, are only seldom ob-served. These fine tumor vessels within the kidney region can therefore only be observed when the angiography is of very 'high quality' and preferably per-formed as a selective study, and when there is advanced atrophy of the re al parenchyma. As in all cases of advanced pressure atrophy of the renal pa n-chyma the renal artery is small and the intrarenal branches displaced. This combination of small and displaced renal arteries and tumor vessels will est b-lish a diagnosis of renal pelvic carcinoma.

Other characteristic changes may be observed at angiography and serv as confirmation of the diagnosis of a growth obstructing the renal pelvis; t us the tumor vessels arise early from the branches of the renal artery because ey



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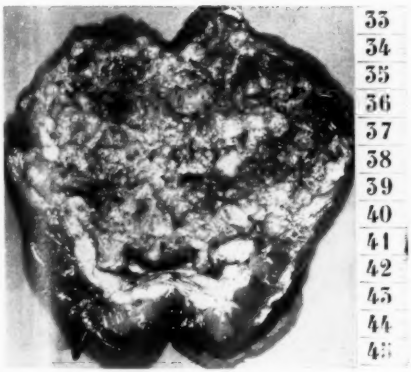

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Fig. 7. Case 8. Papillary carcinoma of left renal pelvis.

a) Operation specimen. Advanced atrophy of renal parenchyma in upper two-thirds of kidney. b) and c) Aortic renal angiography: two arteries supply the kidney. Main renal artery and its intrarenal branches are narrowed, the latter also displaced. Fine tumor vessels are evident in the upper two-thirds of the kidney. No accumulation of medium in upper part of kidney but normal in lower part.

branch from the intrarenal pelvic arteries and not from the peripheral branches as in renal carcinoma.

The width of the renal artery corresponds closely to the reduction of the parenchyma in the common type of hydronephrosis (IDBOHRN 1956, WIDÉN

1958) and there is an accumulation of contrast medium in the parenchyma so that a distinction between the cortex and the medulla is possible. The marked narrowing of the renal artery in the present tumor cases indicated that only a thin layer of renal parenchyma was present; this layer was, however, often thinner than might have been expected with such a small renal artery because the tumor was supplied by the same vessel. There was therefore hardly any accumulation of medium in the parenchyma and the cortex and the medulla could not be differentiated.

Another important difference between hydronephrosis caused by a tumor and true hydronephrosis is the size of the ureteropelvic artery; the widened ureteropelvic artery and the small dorsal artery bear a relationship which is never observed in hydronephrosis not caused by a tumor.

SUMMARY

Ten cases of carcinoma of the renal pelvis studied by renal angiography are reported. The characteristic angiographic appearances produced when the tumor obstructs the urinary flow are described.

ZUSAMMENFASSUNG

Zehn Fälle mit Nierenbeckenkarzinomen, welche mit einer renalen Angiographie untersucht worden sind, werden berichtet. Das für einen Tumorverschluss des Harnabflusses charakteristische angiographische Aussehen wird beschrieben.

RÉSUMÉ

Les auteurs présentent dix cas de cancer du bassinet rénal étudiés par angiographie rénale. Ils décrivent les images angiographiques caractéristiques obtenues quand la tumeur obstrue les voies urinaires.

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DIFFERENTIAL RENAL FUNCTION IN GOLDBLATT TYPE OF HYPERTENSION

Report of a case

by

RICHARD L. SIGGERS

SQUIRE and SCHLEGEL in 1959 reported that urography was ineffective in the investigation of the differential renal function in renal hypertension. Their films were obtained at 5 minutes after commencement of the injection.

It occurred to the present author that the films in the above mentioned investigation had possibly not been obtained early enough, and for that reason a series of 100 normal patients were run in for study. A timing mechanism was started immediately after the beginning of the injection and films were obtained at 1 min, 2 min, 3 min, 4 min, and 5 min. It was noted that in normal patients the kidneys always functioned at the same time, the nephrographic phase occurring at 2 min and the pyelographic phase generally at 3 min. In hypertensive patients, the pyelographic phase could generally be seen at 2 min and was always present bilaterally. The hypothesis was advanced that in Goldblatt kidney there would possibly be a differential function due to renal artery insufficiency, and this was subsequently proved to be true.

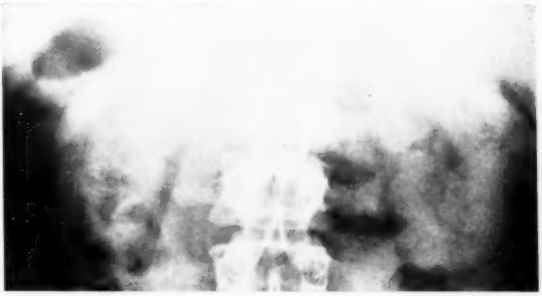
Case report

A 41-year-old man was admitted in our hospital in May 1960 for hypertension of four years duration. Physical examination disclosed no definite cause of the hypertension. The blood pressure was 220/110 mm Hg in the right and left arm and 300/155 mm in the right leg in the recumbent position. The eyes showed minimal arteriolar narrowing. The peripheral pulse equal and strong.

Submitted for publication 15 March 1961.

Urography

Film obtained at 1, 2, 3, and 5 minutes intervals after commencement of injection of Hypaque.



a) At 1 min: Bilateral nephrograms.

b) At 2 min: Contrast medium in calyces, pelvis and upper part of ureter on left side. Right kidney in nephrographic phase.

c) At 3 min: Still some difference in function between the two kidneys.

d) At 5 min: Differentiation between the function capacities of the kidneys, now no longer possible.

Laboratory examination. Hemogram normal; urine analysis negative; BUN 22 mg %; fasting blood sugar 64 mg %; serum potassium 4.5 mEq/l with chlorides 105 mEq/l, and sodium 137 mEq/l with bicarbonate 25 mEq/l. Twenty-four hour urinary catecholamines were 2 gamma per cent. The regetine test and urinary culture were negative. The Fishberg concentration test revealed a maximum concentration of 1 017. The serum creatine was 0.9 mg %.

Roentgen examination of chest: Marked left ventricular hypertrophy with congestive failure. *Urography:* In the 2 min film the right kidney remained in its nephrographic phase while the calyces, infundibula and pelvis of the left kidney were filled. The 3 min film still showed a differential excretion between the two kidneys, while in the 5 min film the function between the two kidneys was almost equal. *Aortography:* Marked stenosis of the right renal artery with post-stenotic dilatation.

At operation: Arteriosclerotic plaque (of the right renal artery, described by the pathologist as a hyaline chondroid plaque.) The blood pressure fluctuated during the postoperative period and five months later averaged 140/90 mm Hg. The patient is now asymptomatic.

At a repeat examination five months after the operation, urography with 1, 2, 3, 4, and 5 min films after the injection of the contrast medium it was shown that there was equal function of the two kidneys.

SUMMARY

A case of renal hypertension due to unilateral renal artery disease is presented. A diagnosis of decreased renal function was suggested by the differences in function observed between the two kidneys in films obtained at 1 min, 2 min, and 3 min after the injection of contrast medium.

ZUSAMMENFASSUNG

Ein Fall mit renalem Hochdruck, bedingt durch einseitige Nierengefässerkrankung, wird vorgelegt. Die Diagnose einer herabgesetzten Nierenfunktion wurde durch die Unterschiede gestellt, welche man auf Röntgenbildern nach einer Minute sowie nach zwei und drei Minuten zwischen den beiden Nieren beobachtete.

RÉSUMÉ

L'auteur présente un cas d'hypertension rénale due à une affection unilatérale d'une artère rénale. C'est la différence observée entre les deux reins sur les films pris au bout d'une, de deux et de trois minutes qui a fait penser au diagnostic de diminution de la fonction rénale.

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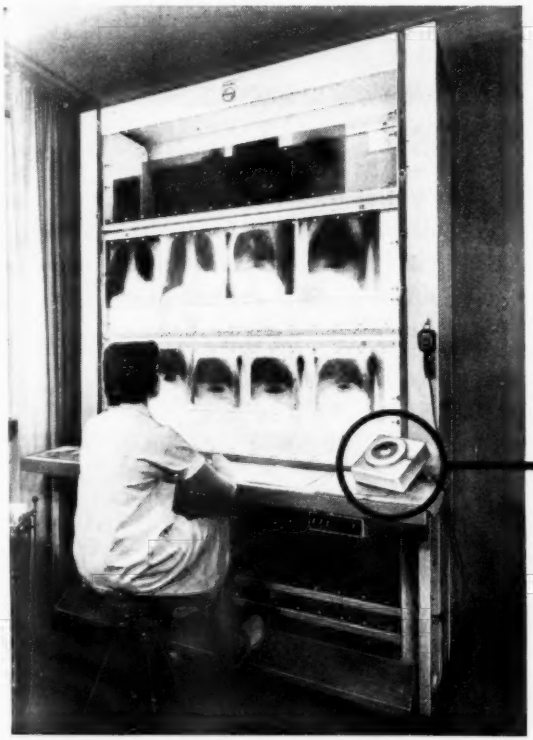

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR: PROF. OLLE OLSSON),
UNIVERSITY OF LUND, SWEDEN.

ARTERIAL COMPLICATIONS IN THORACIC OUTLET COMPRESSION SYNDROME

by

TORD OLIN

The subclavian artery and the brachial plexus in their passage through the cervical region come to lie between the scalenus anterior and the scalenus medius and the first rib. The subclavian vein lies in front of the scalenus anterior but runs more or less parallel to the artery (Fig. 1).

Maladjustment between the thoracic outlet and the plexus or vessels may result in compression of the latter with consequent symptoms. Such compression may be produced by unnatural positioning of the arm or by the presence of a rudimentary or cervical rib. The symptom complexes produced by such compression are called the cervical rib syndrome, the scalenus anterior syndrome, the costoclavicular syndrome, the compression syndrome and the hyperabduction syndrome, according to the presumed aetiology in a given case. It appears that the best 'blanket' term for all these conditions is the one suggested by ROB & STANDEVEN (1958), viz the thoracic outlet compression syndrome. Complications caused by compression of the brachial plexus and the subclavian vein fall beyond the scope of the present investigation and will not be discussed.

Cervical ribs were first mentioned by GALEN, and among those to contribute to our knowledge of such ribs were HUNAULD (1742), and particularly GRUBER (1869), (see KEEN 1907). The literature on the anomaly has since become

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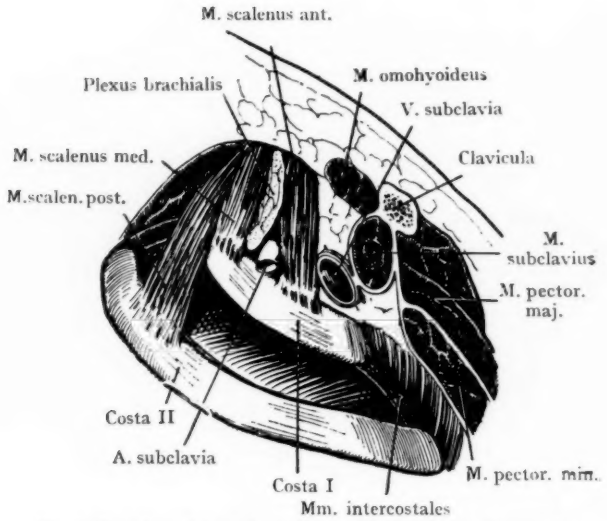

Fig. 1. Drawing of thoracic outlet on right side (from CORNING).

voluminous. In 1818, COOPER & TRAVERS treated the symptoms produced by cervical ribs by conservative methods but the first to report a successful operation in such a case was COOTE (1861), (see EDEN 1939—40); the subclavian artery and the brachial plexus were found to be stretched and compressed as they passed over an exostosis (? a cervical rib) of the first thoracic rib, the artery slightly distal to the exostosis having an aneurysmal dilatation. The anomalous bone was removed with subsequent re-appearance of the ipsilateral pulse and disappearance of the pain in the arm.

During the last two years 3 cases of arterial compression in the thoracic outlet with complicating thrombosis have been diagnosed and treated at our hospital.

Case reports

Case 1. Male aged 52, farmer, was admitted because of a pulsating lump in the right supraclavicular fossa, which he had first noticed one year previously. During the previous month he had also developed numbness and weakness of the right hand, with increasing pain in the fingers on the ulnar aspect. On admission, the right hand was atrophied and the muscles of the arm were weak. The skin temperature began from a few centimetres below the shoulder joint to decrease distally. There was no gangrene.

Roentgen examination. Cervical spine: A rather large cervical rib was present on the right side.

Angiography of the right subclavian artery: A catheter was introduced into the femoral artery but could not be manipulated through the aortic arch into the innominate artery. A catheter (PE 160) was therefore inserted into the right common carotid artery (Fig. 2) and advanced

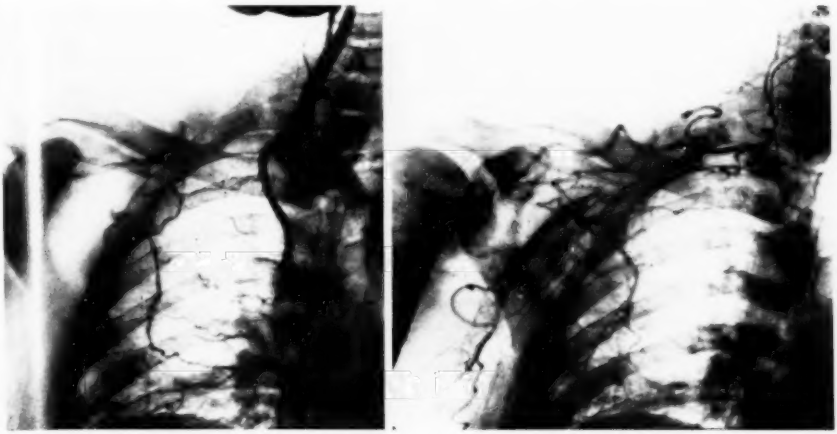

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Fig. 2. Case 1. a) Arteriography. Catheter in right carotid artery. Good filling of tortuous innominate artery, common carotid artery and first part of subclavian artery. Carotid artery manually compressed. Large cervical rib on right side. b) Subclavian artery occluded immediately distal to the origin of internal mammary and vertebral arteries. Several collaterals, especially from the widened internal mammary artery pass out into the arm.

in a retrograde direction into the innominate artery; 15 ml Urografin 60 % were injected by a pressure syringe and serial films obtained. During the injection, the right carotid artery was compressed manually to minimize the flow of the contrast medium into the brain. The innominate artery and the first part of the subclavian artery were widened and tortuous. The subclavian artery was occluded by a thrombus immediately distal to the origin of the internal mammary and vertebral arteries, and the thyrocervical and costocervical trunks. All of these vessels except the vertebral artery gave off numerous collaterals to the arm. Contrast medium from the collaterals had filled a small slit in the axillary artery but otherwise the large artery supplying the arm was packed with thrombi and emboli.

Phlebography. No evidence of abnormality.

Operation. The scalenus anterior was divided and the compressed subclavian artery dissected. A small incision was made in the vessel and parts of the thrombus were aspirated until arterial blood flowed out in a retrograde direction. The skin temperature of the hand was higher after the operation, the pain disappeared and the arm muscles were no longer so weak.

Case 2. Female aged 37, housewife, had had numbness, a feeling of cold and sensory loss of the right arm, especially on the ulnar aspect, for six months. On admission, the small muscles innervated by the ulnar nerve were atrophied. The right radial pulse was weak and the blood pressure in the right arm was 25 mm Hg lower than that in the left. The little and ring fingers were cold.

Roentgen examination. No changes in the cervical spine or the right shoulder.

Angiography of the right subclavian artery (Fig. 3): An opaque catheter was introduced into the right femoral artery and advanced into the innominate artery to the opening of the right subclavian artery; 15 ml Hypaque 45 % were injected and serial films obtained. The subclavian artery proved to be occluded immediately distal to the origin of the internal mammary

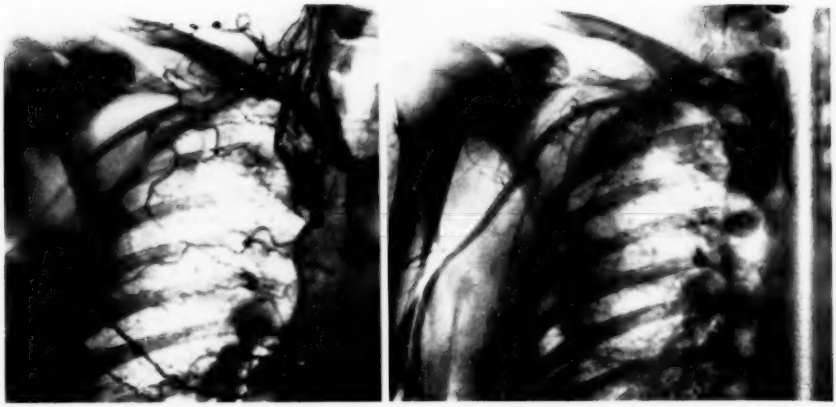

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Fig. 3. Case 2. a) Tip of catheter in right subclavian artery; innominate artery, first part of subclavian artery and common carotid artery contrast filled. Subclavian artery occluded immediately distal to the origin of internal mammary artery. Collaterals to the arm. b) Patent axillary and brachial arteries. S-shaped catheter with tip in subclavian artery well depicted.

and vertebral arteries and the thyrocervical and costocervical trunks. The axillary artery was supplied by collaterals from the internal mammary artery and the thyrocervical and costocervical trunks. The subclavian artery was thrombosed along some 5 cm of its length.

Operation. The cervico-axillary canal was found to be narrow and to contain abundant fibrotic tissue. The subclavian artery, which had degenerated into a rigid cord, contained an old thrombus. The tendon of the scalenus anterior was divided and the nerves and the vessel were dissected.

The patient felt better immediately after the operation but about one year later the vascular and nervous symptoms gradually returned.

Case 3. Male, aged 27, builder's labourer, had for 4 weeks frequently had a tingling sensation in the right hand; this was often followed by pain in the lower arm, especially when carrying heavy loads on the shoulders with the hands over the head. On admission, the right hand was found to be cold and the fingers pale. The right radial pulse was impalpable but pulsations of the brachial artery could be felt in the cubital fossa. Treatment with a stellate block for one week produced some improvement.

Roentgen examination. The cervical spine was normal.

Angiography of the right subclavian and brachial arteries by the same method as in Case 2: widening of the former vessel and small irregularities in the outline of its wall (Fig. 4a); filling defects were present in the distal half of the brachial artery which was completely obliterated along 21 cm of its course (Fig. 4b).

The patient was treated with anticoagulants and massage of the right hand. Gangrene developed in the tips of digs II and III but was rather limited and healed after some small fragments of necrotic tissue had been shed. Treatment was continued for 4 months. The patient returned to work without any appreciable symptoms. At control examination the skin temperature of the right arm and hand was about the same as on the left side. There was no gangrene. The right radial pulse was impalpable.

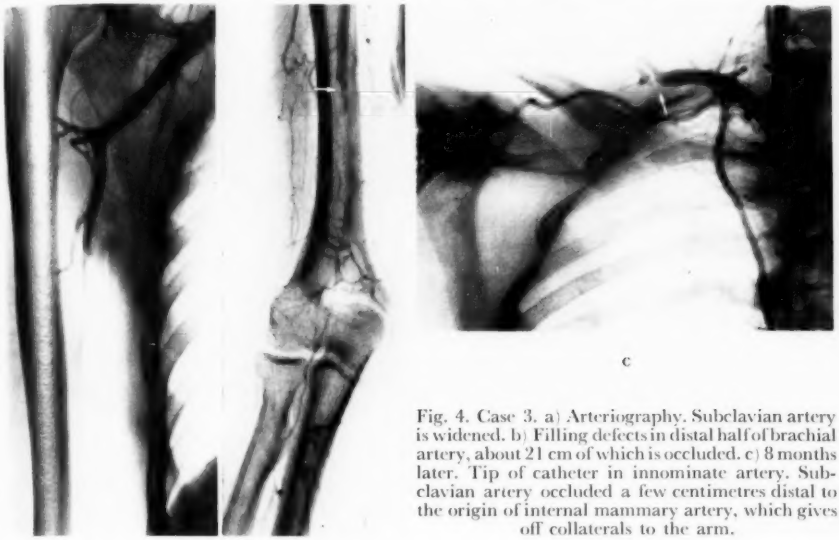

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Fig. 4. Case 3. a) Arteriography. Subclavian artery is widened. b) Filling defects in distal half of brachial artery, about 21 cm of which is occluded. c) 8 months later. Tip of catheter in innominate artery. Subclavian artery occluded a few centimetres distal to the origin of internal mammary artery, which gives off collaterals to the arm.

Angiography of the right subclavian artery 8 months after the first examination (Fig. 4c): The lumen of the middle third of the vessel was occluded for a length of about 5.5 cm. The bulk of the contrast medium passed out into the arm through the collaterals via a widened internal mammary artery and the transverse cervical branch of the thyrocervical trunk. Some 9 cm of the axillary artery were filled via collaterals; the distal part of this artery showed multiple filling defects and was occluded.

Operation. The middle third of the clavicle was resected and the brachial plexus and subclavian artery and vein were dissected free from massive adhesions. The thrombus was removed from the subclavian artery and a satisfactory blood flow re-established.

The postoperative course was uneventful and the circulation and the muscle strength of the right arm improved.

Angiography of the right subclavian artery two months after operation (Fig. 5): The distal part of the subclavian artery was still patent and dilated at the former site of the thrombosis. Angiography was as at the first occasion repeated but with the arm hyperabducted (Fig. 6). The subclavian artery was occluded below the clavicle, as before the operation, and the contrast medium passed into the arm via the collaterals.

Operation. The scalenus anterior was divided.

The patient has felt well after the operation and the arm has almost completely recovered its original strength.

Discussion

Symptoms due to compression of the brachial plexus at the cervico-brachial junction are much more common than corresponding vascular symptoms, and clearly predominate in women (EDEN).

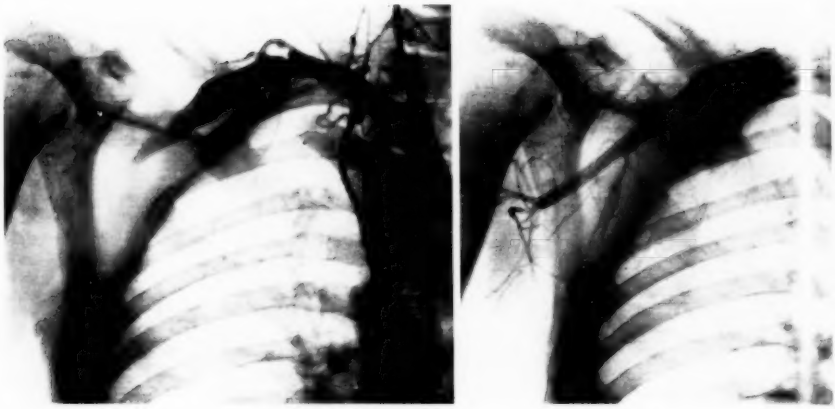

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Fig. 5. Case 3 (same as in fig. 4). a) Arteriography. Thrombus in the subclavian artery has been removed. This part of the artery was also aneurysmatically widened at previous examination. b) Axillary artery occluded distally. Only collaterals pass out into the arm.

Vascular complications in the thoracic outlet, however, occur only slightly more often in women and are about equally common in each arm. According to EDEN only one case has been described (by RUSSEL in 1907) in which both arms were affected. ADSON (1947) was later unable to confirm the statement of EDEN that vascular complications are somewhat more common among manual workers. Most patients have been young or middle-aged although their ages have varied between 5 and 75 years.

Anomalies favouring development of the syndrome

Bones. The cervical rib is the most wellknown abnormality causing the thoracic outlet syndrome. It is often bilateral but may be unilateral without any predilection for one side or the other. The anomaly is more than twice as common in women as in men.

The 1st thoracic rib is sometimes rudimentary (KEEN) and may then cause a compression syndrome in the same way as a cervical rib. The rudimentary rib is about as common as the cervical rib but is usually unilateral (TODD 1912, HAVEN 1939, ETTER 1944, SYCAMORE 1944). The occasional articulation of the 1st thoracic rib is usually of development origin (WHITE et coll. 1945). This articulation, as well as a fracture with abundant callus, may cause compression.

Abnormal ribs are rarely the only skeletal abnormality present (WAKSHE 1951); defects in the vertebral bodies and laminae, with consequent cer[illegible]co-

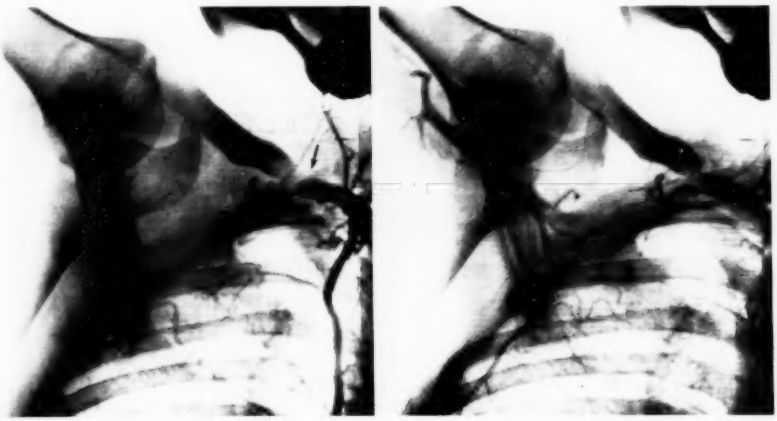

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Fig. 6. Case 3 (same as in figs 4 and 5). a) Examination performed with the arm abducted as much as possible. Subclavian artery occluded where it crosses the clavicle. b) Axillary artery filled only through collaterals and mostly from the internal mammary artery.

thoracic scoliosis, is quite common. In scoliosis of this region the ribs on the convexity are elevated and may contribute to a compression syndrome.

Various changes in the clavicle may also give rise to a compression syndrome, e. g. a fracture with abundant callus, an ununited fracture, or a fracture joined in malposition (POKER et coll. 1958).

Nerves. As pointed out by JONES (1913) the contribution to the brachial plexus from different nerve roots varies with the rib anomalies. The plexus is usually prefixed, i. e. has a contribution from the fourth cervical root and only a small one from the first thoracic root, when a cervical rib is present. If, however, the plexus lacks the contribution from the fourth cervical root and receives a considerable contribution from the first thoracic root, i. e. is postfixed, the first thoracic rib is rudimentary. The degree of prefixation thus varies with the completeness of the cervical rib. When the cervical rib is short, the nerve may be compressed, but if it is a complete rib, the brachial plexus arises from one segment higher up and will not be compressed. The relations of the subclavian artery, however, are not subject to the same sort of variation as those of the nerves and will be more easily compressed by a complete cervical rib than by a small incomplete one (GLADSTONE & WAKELY 1932). This is probably the reason why vascular and nervous complications of cervical ribs often appear separately (Ross 1959).

TODD was of the opinion that the pathologic changes of the arteries arose

from interference with certain sympathetic nerve fibres, but LEWIS and PICKERING (1934) considered the vessel changes to be purely of a mechanical nature.

TELFORD and MOTTERSHEAD (1948) from postmortem investigations described a gripping effect of the median nerve heads around the axillary artery in forced depression of the shoulder. This theory has apparently attracted but little attention by other investigators.

Muscles. Abnormalities of the bones in the thoracic outlet are usually associated with anomalies in the insertions of the scalene muscles. In the presence of a cervical rib, the anterior and middle scalene muscles may have insertions into it as well as into the first thoracic rib. Scalenus medius and posterior may have insertions into the cervical rib alone, or into this and the first and second thoracic rib, or there may be no insertions into a cervical rib. In the case of rudimentary first rib, the scalenus anterior may have two or three slips of insertion into its posterior bony and intermediate fibrous portions.

Both the subclavian artery and the nerve roots may also occasionally traverse the scalenus medius, dividing it into fasciculi. A scalenus minimus may also be present, lying as a slip between the scalenus medius and anterior with insertions into the first rib and, in some instances, the dome of the pleura (see WALSHE).

The most important effect of the scalene muscles in this syndrome is that they probably prevent any forward-downward sliding of the nerve trunks and the artery from the uppermost rib. Reports of successful scalenotomy-operations also point in this direction.

Some authors have described hypertrophy of the scalene muscles, and others a spasm, the artery being compressed by the muscles. The evidence is, however, according to STAMMERS, insufficient.

The different more or less abnormal anatomic structures described are often not enough in themselves to cause the compression syndrome. The age distribution with preponderance for middle-aged women has been interpreted as depending upon the drooping of the shoulders in these patients. The artery is then stretched over the abnormal bone more than early in life.

ADSON pointed out that in the scalenus anterior syndrome the subclavian artery may be compressed still further by inspiring with the head tilted backwards and turned to the affected side.

LEWIS and PICKERING observed in a case of a cervical rib that the clavicle and the cervical rib compressed the subclavian artery when the arm was abducted to 90°. FALCONER and WEDELL (1943) described a costo-clavicular compression syndrome in soldiers carrying heavy packs, the artery being compressed between the clavicle and the uppermost rib; in the position of 'attention' when the shoulders were braced, the radial pulse was occluded in one third of the

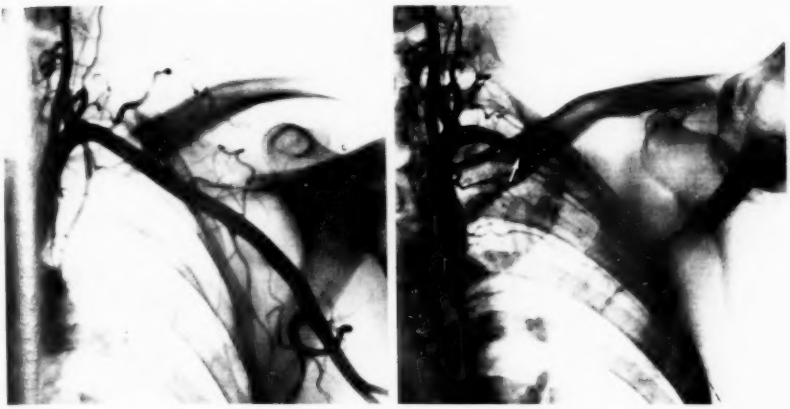

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Fig. 7. Normal appearances of subclavian artery when the arm is to the side (a) but completely compressed under clavicle when arm is abducted (b). Anterior scalenotomy produced no improvement in the appearances.

otherwise healthy individuals. POMMERENKE and RISTEEN (1944) pointed out that in some cases a scalenus anticus syndrome developed after prolonged gynaecologic operations in the Trendelenburg position with the head hyperextended and one of the arms abducted for i. v. fluid administration. WRIGHT (1945) described a neurovascular syndrome produced by hyperabduction of the arm. He studied the effect of hyperabduction on the radial pulse in 150 young men; in one third of them the pulse was easily obliterated and, after rather small adjustments, in as many as 83 %; only in 17 % was the pulse not affected. He ascribed the compression to the passage of the artery under the pectoralis minor and coracoid process or between the clavicle and first rib. The syndrome appeared after prolonged hyperabduction during sleep or work.

According to STAMMERS (1950), Morissey, in students, studied the effect of various positions of the arm on the radial pulse. He confirmed the results of TELFORD & MOTTERSHEAD and found that almost any muscular man can obliterate his radial pulse by active abduction of the arm against the trunk, by the action of retraction (bracing of the shoulders) obliterates the pulse in over 90 % of normal men and women, that active abduction with extension diminishes or obliterates the pulse in about 50 % of normal cases, and that Adson's test was positive in many normal individuals.

STEIN (1946) measured the blood pressure in the arm held in different positions; he often found a lowering of the systolic pressure, though moderate, when the arm was hyperabducted.

We have performed subclavian arteriography in 17 cases (Cases 1, 2 and 5 not included) with the arm at the side as well as abducted as much as the patient could stand for some minutes, i. e. usually not an extraordinarily exaggerated position. In a case diagnosed clinically as a scalenus anterior syndrome of arterial type there was, on abduction of the arm, nearly complete compression of the subclavian artery at the site where it passed under the clavicle, and collaterals were seen. Anterior scalenotomy was performed but at subsequent angiography no improvement was evident (Fig. 7). In 5 cases there was only a slight narrowing of the subclavian artery with no evidence of collateral on abduction of the arm. In 11 cases the artery was not compressed at all on abduction. A narrowing of the subclavian artery in a purely mechanical way can thus be achieved when the arm is held in an unnatural position or in the presence of anatomical abnormalities in the thoracic outlet. Thus it seems unnecessary to resort to more or less elaborate theories about any mechanism interfering with the sympathetic nerves, spasm of the muscles caused by nerve compression, and so on. The reason why the compression syndrome is fairly uncommon is that the exaggerated positions of the arm, often necessary for compressing the artery, are usually not maintained for any longer period of time.

Complications caused by compression of the subclavian artery

A pure compression of the subclavian artery will give only slight ischaemia of the arm as a rich collateral system is easily established. Fibrosis, causing permanent narrowing of the structures passing through the thoracic outlet, will sometimes be produced by small, repeated traumata due to ordinary movements of the arm, neck, diaphragm, and increase the compression of the artery (Case 2). If a thrombosis develops it may occlude some of the collaterals and increase the symptoms and make them permanent (Case 1). Only if emboli are thrown off out into the arm and block arteries more peripherally will the ischaemia be intense (Case 3). Gangrene is often localized only to one finger tip, usually the index finger, even if the block is in the brachial artery and the more peripheral vessels are patent.

Occasionally, though rarely, a thrombus in the right subclavian artery has grown in a proximal direction and occluded the right carotid artery. A block of the inferior part of the vertebral artery will usually give no symptoms as the other cerebral arteries, if normal, will be sufficient for the blood supply to the brain. If, however, the carotid artery is occluded or if emboli are thrown up into the cerebral arteries, hemiplegia or similar serious neurologic complications may result (see HOOBLER 1942). On account of the vascular anatomy a corresponding phenomenon on the left side has never been described.

The subclavian artery is sometimes dilated fusiformly just distal to the narrowing in the thoracic outlet. This aneurysmal dilatation has received much attention and many theories have been propounded. HALSTED (1916) made

Fig. 8. Non-opaque catheter was introduced into the first part of left subclavian artery but recoiled into aorta during injection. Subclavian artery cone-shaped and occluded at the origin of internal mammary artery which is narrow, and most of the collaterals to the arm probably stem from intercostal arteries given off by the thoracic aorta.

fundamental experiments in animals and showed that the poststenotic dilatation became greatest when the lumen of the artery was reduced to about one-third or perhaps one-fourth of its original size. HOLMAN (1954) continued the work of HALSTED and also made experiments with a circulatory model with a pulsating flow, which showed the mechanism of the poststenotic dilatation. The velocity of flow increases at a constriction and when this rapidly ejected stream strikes the more slowly flowing distal stream high kinetic energy is suddenly converted into high potential energy or lateral pressure. The poststenotic turbulent eddies strike the walls of the vessel with alternating high and low pressure waves, which can be palpated as a thrill. After some time the oscillations in pressure result in structural fatigue giving a poststenotic dilatation of the vessel.

A thrombus may now and then be formed in the poststenotic dilatation by the blood platelets being damaged by the turbulent eddies; this may in turn produce emboli in the arm and cause the same symptoms as mentioned.

Roentgen diagnosis

The roentgenologic investigation is first directed towards the skeleton in the thoracic outlet, with special regard to various anomalies and to fractures.

Angiography is however necessary for a correct and detailed diagnosis. ÖDMAN (1950) briefly mentioned a case of scalenus anticus syndrome with cervical ribs. The figures show a bilateral narrowing of the subclavian arteries but no other vessel changes. We generally use Ödman's method with a straight catheter for the left subclavian artery and an S-shaped catheter for the right subclavian

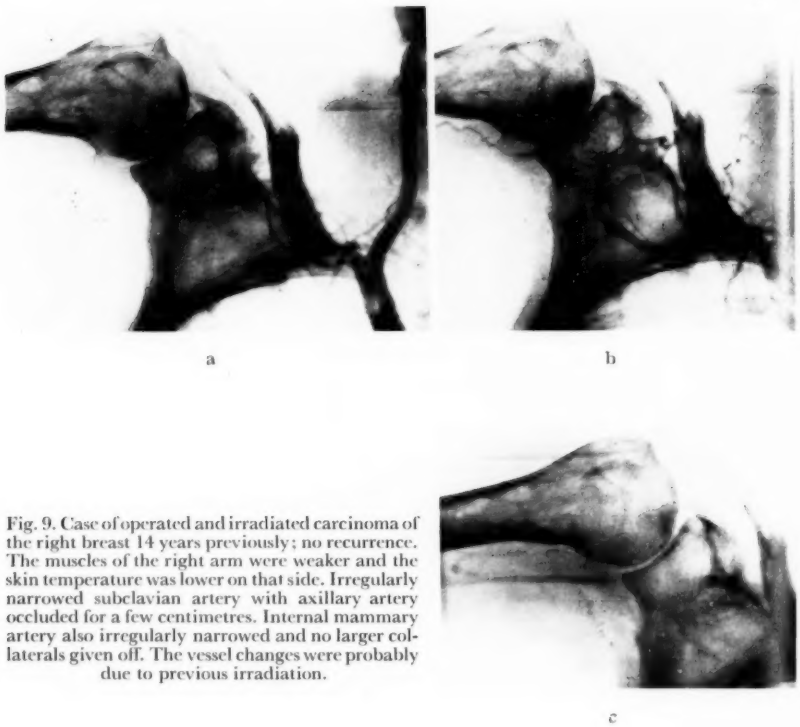

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Fig. 9. Case of operated and irradiated carcinoma of the right breast 14 years previously; no recurrence. The muscles of the right arm were weaker and the skin temperature was lower on that side. Irregularly narrowed subclavian artery with axillary artery occluded for a few centimetres. Internal mammary artery also irregularly narrowed and no larger collaterals given off. The vessel changes were probably due to previous irradiation.

artery; in adults we employ a PE 205 catheter. In elderly patients the catheterization may be difficult, especially on the right side. In such cases the common carotid artery is punctured and a thin polythene catheter (PE 160) introduced against the blood stream down into the innominate artery (Case 1). To prevent too much contrast medium entering the brain circulation, the carotid artery is compressed during its injection (SELDINGER 1957).

Angiography by direct puncture of the subclavian artery was used by CRAWFORD et coll. (1959) but caused a pneumothorax in 20 % of the cases and has not been practised by us. Thoracic aortography has been employed by ECKBOM (1957) and others in cases with impaired blood flow through the subclavian arteries; he placed the tip of the catheter as near the origin of the desired vessel as possible in order to obtain as good a filling as possible of the brachiocephalic arteries. Selective injection directly into the desired vessel however is of course, preferable. STEINBERG (1957) and others used angiocardiography in the in-

ves gation of the subclavian arteries. The quantity of contrast medium given mu be large however and nevertheless the concentration of the contrast me ium in the subclavian arteries will be low; for these reasons the method has nev r been used at Lund.

I trograde catheterization of the subclavian artery from the brachial artery, son times used by us in other cases, should not be used in cases of impaired circ lation of the arm and is also often impossible owing to occlusion of the ves l.

I is necessary to pay due regard to the position of the arm in performing sub avian arteriography. After serial angiography with the arm lying relaxed at the side of body it is often advisable to complete the examination with a new series with the arm in another position, e. g. hyperabducted or with the pati nt in the sitting position with the arm loaded. The history and the clinical exa ination will reveal the position most likely to provoke arterial compression.

Differential diagnosis. Thrombosis of the subclavian artery in the thoracic outlet may of course also be caused by conditions other than a compression syndrome, e. g. atheromatosis, syphilis and brachicephalic arteritis. These will usually lead to wide-spread vessel changes. In brachicephalic arteritis the subclavian arteries are often conically narrowed (WICKBOM 1957) and the collaterals mostly developed from the thoracic aorta via the intercostal arteries and not often from the internal mammary artery or the thyreocervical and costocervical trunks which themselves have a diminished flow (Fig. 8).

Radiotherapy for carcinoma of the breast may produce narrowing of a fair length of the vessel and sometimes thrombosis of the subclavian and axillary artery, but the vessel changes and the location are quite different from those of the compression syndrome (Fig. 9).

Slight narrowing of the subclavian artery occurring when the arm is placed in an unnatural position is of no diagnostic or clinical significance. If, however, complete obstruction appears and collaterals are seen, a compression syndrome may be regarded as present and complications may develop if the position is maintained for any length of time.

An arterial embolus can of course impair the blood supply to the arm, but the embolus is thrown off from some pathologic part of the cardiovascular system, which may then be found. Acute ischaemia of the arm in a case of an embolus cannot be used as a differential diagnostic sign as the first evidence of a compression syndrome may be a brachial embolus (Case 3).

Angiography as well as a thorough study of the subclavian artery in different positions of the arm during operation should clarify the position of the vessel in relation to its surroundings and indicate whether extirpation of some of the bony parts in the thoracic outlet is necessary. Supplementary vascular surgery such as thrombectomy and sympathectomy is sometimes advisable.

SUMMARY

The arterial complications in thoracic outlet compression syndrome is discussed. Three cases are presented. The angiographic technique is mentioned and the diagnostic value of selective subclavian angiography is stressed. Valuable information may be obtained by serial angiography with the arm in various positions.

ZUSAMMENFASSUNG

Die arteriellen Komplikationen im 'thoracic outlet compression syndrome' werden in Kürze studiert. Es werden drei Fälle präsentiert. Die angiographische Technik wird erwähnt und der diagnostische Wert der selektiven Subclavia-Angiographie hervorgehoben. Wertvolle Information kann durch Serienangiographie mit dem Arm in verschiedenen Positionen erhalten werden.

RÉSUMÉ

L'auteur décrit brièvement les complications artérielles du 'thoracic outlet compression syndrome'. Il en présente trois cas. Il décrit la technique angiographique et souligne l'intérêt de l'angiographie sous-clavière sélective. L'angiographie en série dans différentes positions du bras donne des renseignements de valeur.

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HYDATIDIFORM MOLE DIAGNOSED BY PELVIC ANGIOGRAPHY

by

ULF BORELL and INGMAR FERNSTRÖM

The value of pelvic angiography in the diagnosis of hydatidiform mole and choriocarcinoma was the subject of previous papers (BORELL, FERNSTRÖM & WESTMAN 1955, 1958) and the details of the technique of this method of examination were described by FERNSTRÖM (1955). At that time it had not previously been possible to describe in detail the angiographic appearances associated with hydatidiform mole because only one case had been examined by pelvic angiography and the major part of the tumour had then been removed prior to the examination.

Hydatidiform mole has subsequently been diagnosed by pelvic angiography in a further 5 cases. A careful review of the angiograms confirmed the diagnostic value of this method of examination and revealed certain characteristic appearances.

Clinical features. The relevant features of the 5 case histories are summarized in the Table on p. 114.

All the patients were nulliparous and their ages varied between 23 and 29 years.

In most cases the initial sign was vaginal haemorrhage or a blood-stained vaginal discharge, first evident towards the end of the third month of preg-

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Table

Relevant features of the case histories

Case No.	Age	Previous pregnancies	Time of appearance of initial signs*	Size of uterus at time of roentgen-examination	Time of roentgen examination*	Time of delivery*	Delivery	Histological diagnosis
1	29	0	12	Abnormally enlarged	14	22	Vaginal evacuation	Hydatidiform mole
2	23	0	8	Abnormally enlarged	15	16	Abdominal hysterotomy	»
3	25	1 miscarriage	10	Consistent with the duration of pregnancy	19	23	Spontaneous	Not available
4	25	0	13	Abnormally enlarged	17	18	Vaginal evacuation	Hydatidiform mole
5	24	0	12	Abnormally enlarged	13	14	Abdominal hysterotomy	»

* Maturity in weeks.

nancy. With the exception of one case in which the size of the uterus corresponded to the duration of the pregnancy, clinical examination revealed abnormal enlargement of the uterus.

The patients were examined roentgenologically between the thirteenth and nineteenth weeks of pregnancy. For purposes of comparison the angiograms of 30 patients who had been examined between the third and fifth months of a normal pregnancy, were reviewed. All these last patients later underwent therapeutic abortion.

Roentgen appearances

A survey film of the abdomen was taken with the patient supine and the over-couch tube. In order to provide favourable conditions for the demonstration of the foetal skeletal parts, care was taken to avoid superimposition of the maternal bony tissues on the uterus. The tube was therefore angled 15 to 20° caudally. However, in no case was a foetal skeleton identified.

The angiographic appearances differed from those associated with a normal pregnancy; with the exception of one case the intervillous spaces were seen to be fewer in number and more widely separated as compared with those in normal cases.

The contours of the intervillous spaces were also characteristic, being in some places smoothly curved (Figs 1, 2, 5).

Fig. 1. Hydatidiform mole (Case 2). Four seconds after end of injection of contrast medium. The intervillous spaces are clearly visible; they are sparse and some have smoothly curved contours (arrows).

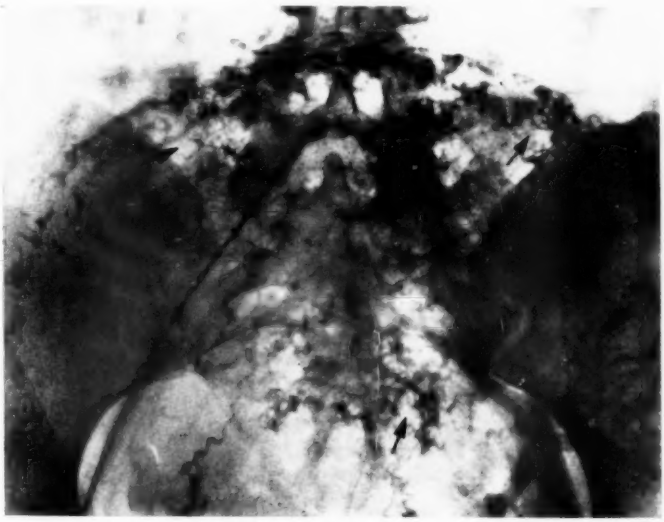

Fig. 2. Hydatidiform mole (Case 3). Four seconds after end of injection of contrast medium. A large number of intervillous spaces, some of which have smoothly curved contours (arrows).

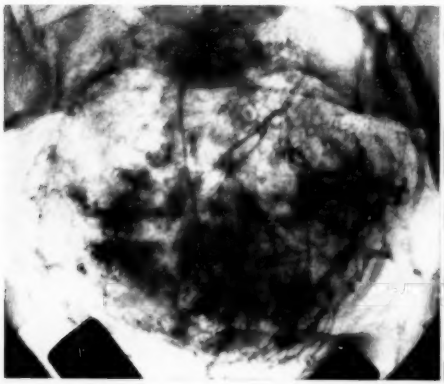

Fig. 3. Normal intra-uterine pregnancy at 4th month. Four seconds after end of injection of medium, numerous intervillous spaces, lying closely together and with irregular and frayed contours.

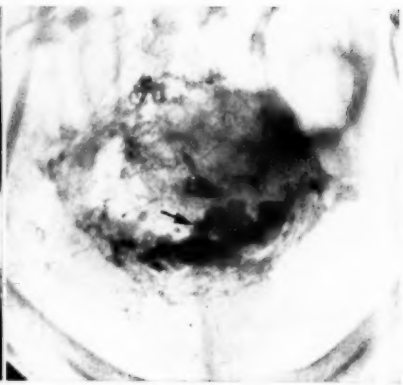

Fig. 4. Missed abortion at 4th month of pregnancy. Four seconds after end of injection of medium, the intervillous spaces are seen in the form of irregular opacities that are not frayed.

The tumour was removed either by abdominal hysterotomy or by vaginal evacuation. The clinical and roentgen diagnoses of hydatidiform mole were confirmed by histologic examination in all but one case (Case 3). In this latter case the concentration of chorionic gonadotrophin in the urine was determined immediately after pelvic angiography and was found to be markedly increased. This also strongly suggested the presence of a hydatidiform mole. Four weeks later the patient, then abroad, was delivered spontaneously and, according to information given by letter, produced a mole. Histologic examination of the tumour was not carried out.

Discussion

The clinical diagnosis of hydatidiform mole may be difficult, the only reliable diagnostic sign being the presence of vesicles in the vaginal discharge. However, this may be a comparatively late manifestation and before the expulsion of vesicles only a tentative clinical diagnosis can be made, usually based on excessive enlargement of the uterus associated with a watery and blood-stained vaginal discharge. The concentration of chorionic gonadotrophin may be a guide to the diagnosis.

Roentgen examination of the abdomen and bony pelvis may often be of considerable value in this condition. The absence of the foetal skeleton in the survey films is a suggestive feature. But as the foetal skeleton is rarely sufficiently calcified to be visible in films taken prior to the sixteenth week of pregnancy a survey film of the maternal abdomen at that time will be of little

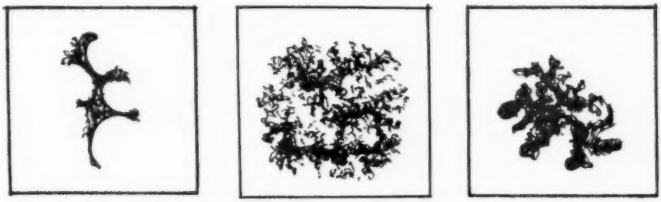

Fig. 5. Schematic representation of intervillous spaces: in normal pregnancy (middle), hydatidiform mole (left) and missed abortion (right).

value in the diagnosis. The absence of foetal parts led to the correct conclusions in the two patients of the present series who were examined roentgenologically after the sixteenth week of pregnancy.

Pelvic angiography enables the diagnosis of hydatidiform mole to be made, irrespective of the duration of pregnancy, because the appearances are already characteristic at a very early stage of gestation, the outstanding features being smoothly curved contours of some of the intervillous spaces (Figs 1, 2, and 5, left sketch); the stroma of the villi undergoes cystic degeneration, which results in the formation of vesicles that vary in size from 1 mm to more than 1 cm and account for the smoothly curved contours of the intervillous spaces. Demonstration of only a small number of intervillous spaces is a further guide to the diagnosis. It is possible that the majority of the intervillous spaces are not outlined because they are filled with vesicles.

In all the cases of the control group, a large number of intervillous spaces with irregular and frayed contours were visible (Figs 3, 5, middle sketch). In certain circumstances, such as missed abortion, the villi undergo necrosis, the intervillous spaces being thereby enlarged. The latter are then demonstrated as relatively large opacities, with irregular contours but not frayed (Figs 4 and 5, left).

A study of the angiographic appearances of the intervillous spaces thus makes it possible to differentiate between normal and oedematous or necrotic villi.

Pelvic angiography has also been found to be helpful in the diagnosis of mole destruens and choriocarcinoma (BORELL et coll. 1955, 1958). This method of examination may prove to be of particular value in cases of intramural choriocarcinoma which are difficult to diagnose clinically. Characteristic features of the angiogram are hypervascularity of the uterus, particularly at the site of the tumour, and irregularly outlined cavities, as well as arteriovenous fistulae within the area of the tumour. The angiographic appearances of mole destruens and choriocarcinoma therefore differ greatly from those associated with hydatidiform mole. This enables the differential diagnosis between these conditions to be made.

The diagnosis of hydatidiform mole would probably be difficult if only a minor degree of cystic degeneration were present because the changes in the villi would be too small to be demonstrated. In such cases the appearances could easily be confused with those associated with a normal pregnancy. For this reason it is advisable to keep the patient under careful observation and to perform further pelvic angiography a few weeks later if the presence of hydatidiform mole is still indicated.

SUMMARY

Pelvic angiography confirmed the clinical diagnosis of hydatidiform mole in 5 cases. Intervillous spaces with occasional smoothly curved contours were a characteristic feature of the condition. The differential diagnosis is discussed.

ZUSAMMENFASSUNG

Eine Beckenangiographie bestätigte in 5 Fällen die klinische Diagnose einer Blasenmole. Die intervillösen Räume mit gelegentlich sanft gekrümmten Konturen waren ein für diese Erkrankung charakteristisches Bild. Die Differentialdiagnostik wird besprochen.

RÉSUMÉ

L'angiographie pelvienne a confirmé le diagnostic clinique de môle hydatiforme dans 5 cas. Les signes caractéristiques de cette affection sont les espaces intervilleux, limités par endroits par des contours courbes réguliers. Le diagnostic différentiel est étudié.

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VARIATION IN SIZE OF SPLEEN INDUCED BY WATER LOAD AS DIAGNOSTIC TEST OF JAUNDICE

by

TORSTEN ALMÉN and LARS ANDRÉN

ANDRÉN (1957) described a splenic reaction test based on the measurement of the organ before and after the ingestion of a relatively large amount of fluid. The normal spleen was found to increase 1 to 2 cm in length on the ingestion of one litre of water, the enlargement disappearing within an hour; in certain diseases including hepatitis no such enlargement was demonstrable. This prompted the present investigation of the effect of a water load on the size of the spleen in a large series of cases of jaundice.

Method. The patients were examined in the prone position with the beam vertical (FFD 1.5 m). One film was obtained before the ingestion of the water, two or three films at short intervals following it, and one film 60 minutes later. Immediately prior to the exposure of each film the patient was given a little soda water in order to ensure that gas was present in the fornix of the stomach; with the fornix filled with gas, the outline of the upper pole of the spleen is easier to define.

Material. The material consisted of 13 cases of obstructive jaundice and 46 cases of hepatocellular jaundice.

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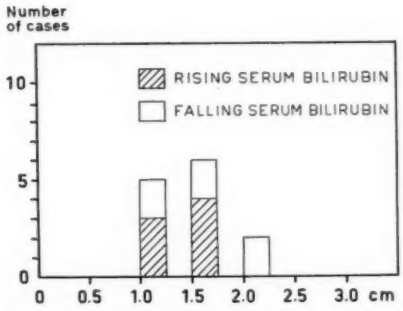

Fig. 1. Increase in length of spleen by water load in 13 cases of obstructive jaundice.

All the patients with obstructive jaundice had a raised serum alkaline phosphatase, and one of the following surgically verified conditions: (1) stone in the common bile duct, (2) stricture of the common bile duct with dilatation of the ducts above the stricture, (3) stone in the gallbladder + dilated common bile duct + biliary stasis and (4) cholecystitis + cholangitis + a dilated common bile duct containing thick bile.

Of the 46 cases of hepatocellular jaundice the condition was due to epidemic hepatitis in 43, to inoculation hepatitis in 2 and to drug (Marsilid) poisoning in 1. The diagnosis of epidemic hepatitis was based on a known exposure to an epidemic, to clinical features, to a raised serum transaminase or other signs of hepatocellular damage, and in 2 cases on liver biopsy.

The spleen increased in length by at least 1 cm in all the 13 cases of obstructive jaundice following the ingestion of the water, seven of the cases being examined while the serum bilirubin was rising and six while it was falling (Fig. 1). The length of the spleen averaged 13 cm (range 10 to 16 cm).

Thirteen of the 46 cases of hepatocellular jaundice were examined while the serum bilirubin was rising, and in 10 the length of the spleen remained unaltered, or increased at the most by 0.5 cm and in 1 case by 1 cm (Fig. 2); in these cases the length of the spleen averaged 16 cm (range 12 to 23 cm). The remaining 33 cases were examined while the serum bilirubin level was returning to normal; in 8 the spleen increased in length by less than 0.5 cm, in 7 by less than 1 cm, while in 18 cases the spleen reacted in a normal way, i. e. it increased by more than 1 cm. The length of the spleen before the test in these 33 cases averaged 14 cm (range 10 to 18 cm).

Seventeen of the cases of hepatitis were examined on two occasions at an interval of 1 to 12 weeks. Fifteen patients recovered from their jaundice and in all of them the spleen was smaller on the second occasion; in 11 of them the spleen reacted more markedly to the second test. In 2 patients the spleen was larger on the second occasion and reacted less strongly to the test. Both of these had a recurrence and one died in hepatic coma.

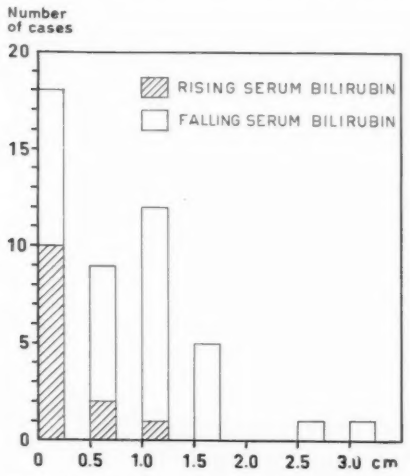

Fig. 2. Increase in length of spleen by water load in 46 cases of hepatocellular jaundice.

Results

All of the cases of obstructive jaundice reacted to the test in a normal way, i. e. an increase of more than 1 cm in the length of the spleen. Two cases were subjected to surgical exploration for probable obstructive jaundice. In neither of them was the water load followed by any increase in length of spleen and the test was thus against obstructive jaundice. In both cases the bile ducts were of normal appearance and liver biopsy showed liver necrosis. Of the 13 cases of hepatocellular jaundice examined while the serum bilirubin was rising, only one reacted in a normal fashion to the water load, while in all the cases of obstructive jaundice the water load was immediately followed by elongation of the spleen by 1 cm or more.

In the cases of obstructive jaundice the average length of the spleen was not so great as in the cases of early hepatitis (13 cm against 16 cm). In the cases of hepatitis which healed and which were examined twice, the length of the spleen was less, and the organ reacted more markedly to the water load on the second occasion than on the first.

Discussion

ÅSDRÉN (1957) offered the following tentative explanation for the reaction of the spleen to the water load: 'The ingestion of such a relatively large amount of water may increase the flow of the blood through the portal system and thereby the portal pressure. This possibility is supported by the finding that

the enlargement diminished considerably or disappeared as soon as the subject assumed the erect posture. The decrease in size on change of posture is probably due to a decrease in hydrostatic pressure in the splenic vein'. ATKINSON & SHERLOCK (1954) and DAVIS et coll. (1954) showed that the intrasplenic pulp pressure closely reflects the portal pressure.

REICHMAN and DAVIS (1957) stated that the intrasplenic pressure as measured by puncture is increased in the acute phase of hepatitis but is on the average one third lower during convalescence.

The increase in the portal pressure may be responsible for splenomegaly in the early stage of hepatitis, an increased tension of the capsule of the spleen preventing the normal reaction of the spleen to an increased flow of blood through the vena porta. On regression of the hepatitis, portal stasis regresses, the enlargement of the spleen decreases, and the spleen is then again able to react in a normal way to variations in the portal pressure induced by the water load.

ARONSEN and NYLANDER (1960) have shown in dogs that contrast medium injected for lienoportal venography passes through the liver quicker when the common bile duct is ligated suggesting that such ligation does not produce portal stasis. This fits in well with our observations that in human subjects with obstructive jaundice the spleen reacted in a normal way to the water load.

The investigation provides support for the assumption that the changes in the size of the spleen following the ingestion of a relatively large amount of water are due to changes in the portal pressure.

The water load test is thus a useful tool in the differential diagnosis of jaundice, and is of value in following the course of hepatitis. The spleen is enlarged in the acute phase of hepatitis.

SUMMARY

Application of the water load test of the spleen in a series of 59 cases of obstructive and hepatocellular jaundice proved that the test is reliable in the differentiation between these two types of jaundice and that the spleen is enlarged in the acute phase of hepatitis.

ZUSAMMENFASSUNG

Anwendung der Wasserbelastungsprobe der Milz hat sich in einer Serie von 59 Fällen von obstruktiver und hepatozellulärer Gelbsucht in der Differenzierung dieser zwei Gelbsuchtstypen als zuverlässlich erwiesen und ergeben, dass die Milz in der akuten Phase der Hepatitis vergrössert ist.

RÉSUMÉ

L'application de l'épreuve de surcharge hydrique de la rate dans une série de 59 cas d'ictère par rétention et par hépatite a montré que cette épreuve est fidèle pour différencier ces deux types d'ictère et que la rate est augmentée de volume à la phase aigüe de l'hépatite.

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EXPERIMENTS WITH LITHIUM IN CHEMOTHERAPY OF CANCER

by

JØRGEN HASTRUP

A constantly increasing number of patients in the manic phase of manic-depressive psychosis have been treated with lithium during the last 10 years.

Professor F. H. Shaw, the pharmacologist of Melbourne, visited the Institute of General Pathology in 1958. He mentioned that an antineoplastic effect of lithium had been observed in patients with manic-depressive psychosis who also suffered from cancer and suggested that these observations might be investigated.

It has repeatedly been shown that lithium is capable of inducing a growth change in embryonic tissue, e. g. sea-urchin eggs, resulting in developmental anomalies. In addition, lithium interferes with metabolic processes in various tissues through a change in the catalysis of reactions in which energy-rich bonds change places. (For a survey of the pharmacologic and biologic properties of lithium the reader is referred to SCHOU 1957.)

According to CHÈVREMONT-COMHAIRE 1953, lithium is able to change the growth curves for chick fibroblasts and myoblasts in tissue culture and gives rise to a prolonged metaphase and the development of cells with abnormal nuclei. TRAUTNER et coll. showed that the administration of lithium reduces the number of corpora lutea in pregnant rats, and interpreted this observation as a result of a growth-inhibiting effect of lithium on the rapidly proliferating

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tissue in the ova and follicles. This paper deals with the investigations of the antineoplastic effect of lithium both in animals and clinical experiments.

Animal experiments. The action of lithium was studied in a lymphatic leukaemic tumour, NJ, in AKA mice and in an adenocarcinoma, PBH, in C_3H mice. Both these tumours are homologous since they have arisen and been retransplanted in the respective inbred mouse strains. The transplantation of the tumours was performed by the subcutaneous injection of approx. 10^6 tumour cells into the right axilla, all injections resulting in 'takes'. Lithium was given by daily intraperitoneal injections of LiCl prepared from the stable Li_2CO_3; the control animals were given similar injections of NaCl. In the experiments with the lymphatic tumour NJ, lithium was administered in doses of 2.5 mEq/kg and 5.0 mEq/kg daily.

The low dose, given from the first day after transplantation, had no influence on the survival time of the animals which like the control animals died in from 11 to 13 days. When the dose was increased to 5 mEq/kg daily, given from the fourth day after transplantation, the treated animals died before the controls. Uninoculated AKA mice tolerated 5 mEq/kg daily for more than 20 days without the development of any toxic symptoms. In similar experiments with the adenocarcinoma PBH, even the low dose of 2.5 mEq/kg daily killed the treated animals in about 20 days while the controls lived for about 28 days; in toxicity experiments on uninoculated animals this dose was tolerated for more than 40 days. The high dose of 5 mEq/kg daily that was commenced later in the experiment, likewise exerted only a toxic effect and killed the animals in about 16 days after the transplantation. All animals which succumbed were studied histologically, but no changes in the composition of the tumour, metastases or leukaemic infiltrations into the organs of the animals were demonstrated.

The tumour size was followed in both series of experiments. In the experiments with NJ leukaemia, no difference in the size of the tumours in the treated animals and the controls could be demonstrated but in those with the PBH adenocarcinoma, the tumours grew more slowly in the treated than in the control animals. However as the former lost weight more rapidly than the latter, no significance can be attributed to the lower tumour growth rate in the treated animals in the evaluation of the effect of lithium since a certain relationship exists between the nutritional state of the animals and the tumour growth.

Further experiments were performed with the tumour types tabulated below:

Designation	Type of tumour	Mouse strain
JBI	Reticulosarcoma	C_3H
Krebs II	Anaplastic carcinoma	AKA
GH	Adenocarcinoma	Street
Ehrlich	Carcinoma	C_3H

Lithium given in daily doses of 3 mEq/kg, however, did not prolong the survival time of the mice or inhibit the tumour growth in these experiments.

It appears from these data that lithium exerted no antineoplastic effect on the mouse tumours studied. It is worth noting that the tumour-bearing animals did not tolerate lithium so well as similar healthy animals. SIMON, TRAVERNER and COATS have recently reported an experiment in which they found that mice with an Ehrlich ascitic tumour retained larger amounts of lithium than the control animals, both after subcutaneous and oral administration. In the present experiments, no Li analyses were carried out on the tumour-bearing animals. Serum analyses (performed in the Biochemical Laboratory of the State Mental Hospital, Aarhus) during the toxicity experiments gave results similar to those obtained by SCHOU after treatment of rats with toxic doses of lithium. These animals died from renal damage (upper-nephron nephrosis).

Clinical experiments. A small group of patients with malignant disorders, as given below, were treated with lithium, during which period they received no other form of specific therapy.

Malignant disorder	No. of patients
Myelomatosis	4
Hodgkin's disease	4
Lymphosarcoma	2
Carcinoma of the breast	1
Carcinoma of the kidney	1
Mycosis fungoides	1

None of these cases revealed a favourable effect which could reasonably be ascribed to lithium; on the other hand, certain side-reactions were observed.

Manic patients are usually given an initial dose of 1 800 mg Li_2CO_3 daily, followed by a maintenance dose of 600 to 900 mg daily. It soon appeared that patients with malignant disorders were unable to tolerate these high doses. This is illustrated by the following brief case history:

A woman, aged 25, had suffered from Hodgkin's disease since 1955 and had been treated with several courses of roentgen irradiation, d-l-diepoxybutane, T. E. M., and phenylbutazone. On admission on 10 October 1958, she was acutely ill with high fever; she had an enlarged spleen and was troubled by itching of the skin and nausea. Haemoglobin (after three transfusions) 62 %, creatinine clearance 88 ml/min, weight 60 kg. The patient showed marked intolerance to alcohol (BICHEL). On 27, 28, and 29 October, she was given Li_2CO_3, 300 mg × 4. The next day the patient complained of a feeling of weakness in the limbs, accompanied by tremor of the hands. Serum Li was determined as 2.47 mEq/l (a value exceeding 2.0 mEq/l may be toxic); accordingly, the dose was reduced to 300 mg × 2. On 31 October only 300 mg Li_2CO_3 were given, but confusion, marked tremor and sopor developed, gradually falling into coma. The patient was still unconscious the following day although the serum Li after parenteral fluid therapy, chiefly with NaCl, had fallen to 1.28 mEq/l. On 2 November the serum Li had fallen to 1.00 mEq/l, and the patient was awake and could drink water unaided. During the next few days, her condition improved, and on 5 November she responded rationally to questions, although her speech was still slow and slurred. The serum Li was now 0.2 mEq/l.

Te lays later, Li_2CO_3 treatment was resumed, with 300 mg daily, but as mental dullness, polyu and excessive thirst accompanied by a coarse tremor and muscular fasciculations devel ed after about 10 days the treatment was discontinued. During the latter period of treat nt the serum Li was at a maximum of 0.56 mEq/l.

Sl ht symptoms of lithium intoxication developed in several other patients, in sp e of small doses and a relatively low serum Li level.

Th ee patients had certain peculiar hallucinatory experiences during the lithiu treatment. A 34-year-old man with lymphosarcomatosis stated at a time hen his serum Li occupied a level of from 1.10 to 1.50 mEq/l that he had a feeling as though he were lying on his left side in the bed, although from his p ition in relation to the room, he realised that he was acutally lying on his ri ht side. He also thought he had seen someone (the author) get up from a chair t the bedside and walk round the bed back to the chair; he afterwards realis d that these observations were not founded upon objective reality. He had s milar fleeting impressions during the following two days. Two other male patien s, aged 44 and 61, both suffering from myelomatosis, had hallucinations, which had certain features in common, during a course of lithium therapy given in the out-patient department. They thought they had seen and spoken to people both known and unknown who had appeared in their homes in the evening or at night. One of the patients even went so far as to send the 'visitors' away and lock the front door behind them. These experiences seem to have occurred in the dark, and it is very difficult to distinguish between them and dreams.

It may be concluded from these few clinical experiments that lithium has no therapeutic effect on the disorders concerned. Specific changes in the blood were not demonstrated. The side-reactions may perhaps be partially ascribed to the relatively poor general condition of the patients; similar violent reactions to lithium therapy have not been observed in the State Mental Hospital at Aarhus, where a large number of manic patients have been treated with lithium.

It is difficult to assess the hallucinatory experiences of the three patients; it is beyond dispute that they occurred during lithium treatment and disappeared when this treatment was discontinued. One of the patients was subjected to a psychiatric examination by Dr Strömgren who concluded that the experiences seemed to be of a hypnagogic origin; the possibility that the lithium may have been a contributory factor in their development cannot, however, be excluded. No reports on observations of similar hallucinatory experiences are available in the literature, but BLEULER of Zürich has recently informed us that he had observed genuine hallucinations in one patient during lithium therapy: "Die Patientin halluziniert lebhaft Mücken, optisch und mit dem Hautsinn."

Acknowledgement

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SUMMARY

The treatment with lithium of malignant homologous mouse tumours and of 13 patients with malignant disorders produced no antineoplastic effects. A diminished tolerance to lithium was observed both in the tumour-bearing mice and in the patients.

ZUSAMMENFASSUNG

Die Lithiumbehandlung von bösartigen homologen Mäusetumoren und von 13 Patienten mit malignen Störungen erzeugte keine antineoplastische Wirkung. Eine Herabsetzung der Lithiumtoleranz wurde sowohl bei den tumortragenden Mäusen als auch bei den Patienten beobachtet.

RÉSUMÉ

Le traitement par le lithium de tumeurs malignes homologues chez des souris et d'affections malignes chez 13 malades n'a eu aucun effet antinéoplasique. On a constaté une diminution de la tolérance au lithium chez les souris porteuses de tumeurs et chez les malades.

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EVALUATION OF THE PLACEBO EFFECT IN THE TREATMENT OF RADIATION SICKNESS

by

JOHN A. PARSONS, JOHN H. WEBSTER and J. E. DOWD

In a recent study made in the Department of Radiation Therapy of this Institute, it was found that 61 to 72 % of all patients suffering from so-called radiation sickness would respond favorably to placebo medication. A few years ago, the drug literature was suddenly flooded by an increasing number of drugs of purported value in the treatment of radiation sickness. Although this syndrome had never been considered a problem in this department, it was felt that an evaluation of the comparative effectiveness of these drugs might be desirable. Another important factor to be considered was the variable cost of these drugs. Prior to this, the drug of choice in the treatment of patients developing radiation sickness was pyridoxine. This drug, although maintaining a degree of popularity in many centers (MAXFIELD 1943, and SHORVAN 1949), has proven rather costly to the patients.

A double blind study was therefore designed to compare eight different drugs, each purported to be equally effective in the treatment of radiation sickness, but before proceeding with the study, it was deemed necessary to explore certain aspects of methodology and to evaluate certain variables of possible consequence to the determination of drug effects.

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The patients were grouped according to whether they were receiving radiation below or above the diaphragm. No attempt was made to classify the patients according to the size of the field irradiated or the daily dosage. This would divide the patients into groups too small to study; the influence of these factors could be evaluated at the conclusion of the study.

A variable of possible equal importance might be the day of the week on which a patient first experienced symptoms, as patients treated in this department receive radiation therapy Monday through Friday; the day of onset of symptoms might thus provide a rough index of the amount of exposure to irradiation after a period of rest (i. e. the week-end). The total radiation dosage, prior to experiencing symptoms, may also conceivably contribute to symptom severity.

The probable existence of a large proportion of placebo reactors in the treatment and control groups among patients reporting symptoms of radiation sickness would reduce observed differences and obscure real effects. This influence could be obviated by excluding placebo reactors, or it could be eliminated by numerical adjustment. Exclusion depends upon the use of a screening procedure, and a variety of specific procedures are possible. Numerical adjustment depends on having a reliable estimate of the proportion of placebo reactors, but the existing literature does not provide such an estimate. It was therefore decided to set up a methodologic study preliminary to the systematic evaluation of drug effectiveness in relieving symptoms of radiation sickness. It was decided to employ a known anti-emetic (prochlorperazine-SKF, kindly supplied as 'Compazine' by Smith, Kline and French Laboratories), 5 mg and 10 mg t. i. d. along with placebo medication (Lactose), with the following objectives in view:

1. To estimate the proportion of placebo reactors among patients reporting symptoms of radiation sickness.
2. To determine the extent to which the proportion of placebo reactors is related to: (a) the locus of irradiation (i. e. above and below diaphragm), (b) the day of onset of symptoms, (c) the order of treatment with placebo and trial anti-emetic compounds.
3. To evaluate, if possible, the effectiveness of prochlorperazine as an anti-emetic for radiation sickness and determine the extent to which its efficacy is related to: (a) patient classification variables, (b) the order of treatment with placebo and trial compounds, (c) dose (5 mg vs 10 mg t. i. d.).

Method of study

Although the syndrome of radiation sickness is said to include a variety of symptoms: nausea, vomiting, anorexia, malaise, prostration, headache, dizziness, and weight loss, it was felt that we could accurately base our diagnosis only on the first two (i. e. nausea and/or vomiting). In deference to the plea

Table 1

Pattern of medication

Day entering study	Envelope No. 0	Envelope No. 1	Envelope No. 2	Envelope No. 3
Monday	0	Drug trial No. 1 for 3 days	Placebo for 4 days	Drug trial No. 2 for 3 days
Tuesday	0	for 3 days	» for 3 days	for 3 days
Wednesday	0	for 3 days	» for 2 days	for 3 days
Thursday	Placebo for 4 days	for 3 days	» for 4 days	for 3 days
Friday	» for 3 days	for 3 days	» for 4 days	for 3 days

of other authors (ELLIS and STOLL) it was decided to attempt to evaluate the symptoms of anorexia and lassitude individually.

It has never been our practice to give anti-emetics throughout the course of radiation therapy as a prophylactic measure against radiation sickness. We do not agree, furthermore, that this eliminates the psychic element as stated by other authors (SILVERMAN et coll.).

Any patient receiving radiation therapy to any area of the trunk at our institute and reporting symptoms of radiation sickness was eligible for inclusion in this study. A patient was excluded only when the radiation sickness was judged so severe as to interfere with the course of radiation therapy.

Subjects were classified on the basis of two variables: locus of radiation (above or below the diaphragm) and day of the week entering study. Accordingly, there were ten subject groups: two for each of five days. Patients could not enter the study on Saturday or Sunday.

A placebo compound (Lactose) and two dosage levels (5 and 10 mg) of prochlorperazine were used as treatment drugs. All were prepared in No. 2 pink capsules, and dispensed in envelopes distinguishable only by number. A drug trial consisted of three capsules daily on three consecutive days.

Every subject was to experience a three-day trial of two different compounds: one of placebo and one of either 5 mg or 10 mg of prochlorperazine. Both orders of these two drug combinations were used equally often. The resulting four treatment groups are identified by letter below:

Group	First trial	Second trial
A	Placebo	5 mg prochlorperazine
B	5 mg prochlorperazine	Placebo
C	Placebo	10 mg prochlorperazine
D	10 mg prochlorperazine	Placebo

Placebo capsules were given on certain days in addition to the trial period, as shown in Table 1.

The use of placebo capsules on week-ends and initially for patients entering the study on Thursday or Friday was known to the medical staff; however, it

Table 2

Patients excluded from study

Reason for exclusion:	Site of radiation		Total
	Above diaphragm	Below diaphragm	
Did not follow instructions	2	3	5
Complications in patient's condition	3	0	3
Response pattern to pills not interpretable	2	0	2
Unreliable history of symptoms	0	1	1
Radiation therapy discontinued	1	2	3
Patient refused to continue medication	0	1	1
Total	8	7	15

was not known to them that in any of the drug trials placebo capsules were also used. Before starting the second drug trial, the patient was withdrawn from the study for a period of at least 48 hours if his symptoms had disappeared. If symptoms reappeared the second drug trial was begun.

Patients were allocated to the treatment groups as follows: within successive sets of four individuals, one was randomly assigned to each treatment group, and assignment in one subject category was independent of every other. The order of assignment of patients to treatment groups was not known to the medical personnel. Treatment was assigned by taking the first unused envelope from an appropriate prearranged set. Ten sets of envelopes, one for each subject category, were used.

The envelopes were identified only by serial number and subject category, each containing the correct number of capsules to supply one patient throughout the study period.

The patients were interviewed daily throughout the course of study to obtain an evaluation of symptom severity and toxic effects. Evaluations were recorded on individual forms prepared for this purpose.

Results and Discussion

An attempt was made to evaluate the symptoms of anorexia and lassitude individually, and in combination with the symptoms of nausea and vomiting. This proved to be unproductive in large part because many of the patients had suffered from these symptoms for some time preceding the onset of radiotherapy. In some cases this could be ascribed to the extent of the disease and in some to their apprehension in the knowledge that they suffered from malignant disease. Therefore, the results reported are based on relief of the symptoms of nausea and vomiting.

Of the 126 patients who initially displayed symptoms of radiation sickness, only 52 completed the series of two drug trials. Fifteen patients were excluded

Table 3

Patients not completing sequence of drug trials

Reason for not completing study:	Site of radiation: Above diaphragm	Below diaphragm	Total
No recurrence of symptoms between trials	7	24	31
Radiation therapy discontinued	5	13	18
Complications unrelated to drug therapy	2	3	5
Patient refused further medication	0	2	2
Did not follow instructions	0	2	2
Patient expired before study ended	1	0	1
Total	15	44	59

from the study for the reasons shown in Table 2 and do not appear again in any further tabulations or in any of the conclusions drawn about placebo or drug effects.

Of the remaining 111 patients, who completed at least one drug trial of the sequence and who contributed usable information to the study, 59 did not complete the full sequence of trials. The reasons for this attrition of the series through noncompletion are given in Table 3. As seen, the most frequent cause of noncompletion is the failure of the patient to redevelop symptoms of radiation sickness between drug trials on days when no pills were given. If no further symptoms developed when the medication was withdrawn, the trial was stopped since there were no symptoms against which to evaluate drug response. The 18 patients who discontinued radiation therapy before completion of the drug trial were those who did not develop symptoms of radiation sickness until later in the course of radiotherapy, or those who had courses of radiotherapy shorter than originally foreseen. Of the complications, there were four cases of severe and protracted vomiting (three irradiated below the diaphragm) and one case of cardiac decompensation.

A patient was deemed to have an unequivocal response (++) if his or her symptoms of radiation sickness disappeared during administration of any one compound. No response was recorded as (——). As seen from Table 1, patients entering the study on Thursday or Friday received an initial few days of placebo medication and then proceeded with Drug trial 1. Since all patients completed at least the first Drug trial plus Envelope 2 of placebo medication, it was possible to obtain an indeterminate response. If there was any doubt about the response of a patient to medication, this was recorded as (+—). This situation arose when symptoms disappeared during administration of one compound, were held in abeyance during the administration of the succeeding compound, and then did not reappear when all medication was withdrawn. This occurred in twenty cases. If a similar study were to be conducted in the future, we feel it would be advisable to allow a lapse

of time between each medication whenever symptoms disappeared during administration of the first medication. This would eliminate the indeterminate groups.

In the series of 52 cases, who completed the entire sequence of drug trials, there were two patients who responded completely to the initial placebo medication started on Thursday or Friday, and did not redevelop symptoms before starting Drug trial 1 on Monday. Response to prochlorperazine in Drug trial 1 is therefore considered ambiguous. Two cases in this group were also inadvertently started on Drug trial 2 without a lapse of 48 hours without drug to see if symptoms would reappear. Both of these cases received placebo medication in Drug trial 2, and since their response had been interpreted from previous medication, this trial was disregarded.

In the series of 59 cases who did not complete the entire sequence of drug trials, but did complete the first drug trial, some information can be obtained from each patient. Again, six patients entering the study on Thursday or Friday responded completely to the initial placebo medication and therefore their response to prochlorperazine given in the first drug trial is considered ambiguous. Ten patients responded completely to prochlorperazine in the first drug trial, and therefore their response to the placebo spacer (Envelope 2) was considered ambiguous, even though they did not redevelop symptoms when all medication was withdrawn. In the entire series, there were 78 patients in whom a response to both prochlorperazine and the placebo could be evaluated. Fifty-one (65.5 %) responded to the drug, but many of these also responded to the placebo. Eight (10 %) were classified as an indeterminate response. Nineteen cases (24.4 %) showed no response to the drug. Thirteen of this latter group showed no response to placebo either, but six cases were classified as placebo reactors.

On further review of these six cases, it is felt that in only one case was there an unequivocal response to placebo and an actual increase in symptoms when the patient was receiving prochlorperazine. This seeming contradiction may be explained by the fact that the radiation dosage was increased the day prior to the switch to prochlorperazine. Two of the remaining five cases experienced very mild nausea while receiving prochlorperazine, for which they were classified as non-reactors. The three other cases responded to placebo at one point but failed to respond to placebo at another point. These might have been classified as indeterminate responses.

Placebo reactors. Response to placebo medication given initially to those patients entering the study on Thursday or Friday could be classified as effective (++) or ineffective (— —) depending upon whether symptoms disappeared or remained. Response to placebo medication given after Drug trial 1 as a spacer could be judged effective only if the patient still experienced symptoms after Drug trial 1. If the patient did not have symptoms on the

Table 4

Percentage of placebo reactors classified by site of radiation

Site of radiation	No. of patients	Percentage placebo reactors		Average cumulative integral dose of radiation received (megagram rads)
		++ only	++ and +−	
Above diaphragm	30	70.0	76.6	7.1
Below diaphragm	81	58.0	70.3	11.5
Total	111	61.3	72.1	10.3

completion of this trial, but redeveloped symptoms during the placebo spacer, then the placebo was judged ineffective. The possibility of an ambiguous response (+−) has already been discussed. Computations of the proportion of placebo reactors are based on both the (++) group and a combination of the (++) and (+−) groups.

Placebo effect and site of irradiation. The percentage of placebo reactors for the total series classified by the site of radiation is shown in Table 4. The percentage of placebo reactors in the 111 patients ranges between 61 and 72 depending on whether or not the (+−) group is counted. The true percentage of placebo reactors for this sample of 111 patients lies somewhere between these two percentages. Since this series of 111 patients may also be regarded as a sample from some population of radiation therapy patients sampled through time it would be possible to compute confidence limits for the percentage of placebo reactors in this conceptual universe. However, because of the presence of the indeterminate group, we have not attempted to compute confidence intervals for the group as a whole or for any subgroups.

The percentage of placebo reactors is seen to be higher for those radiated above the diaphragm. While this difference is not statistically significant even when we use the most extreme estimates of percentage placebo reactors for the two groups (76.6 % for the group radiated above the diaphragm and 58.0 % for the group radiated below the diaphragm), the difference in rates shows a relationship with the average cumulative integral doses of radiation received by each group (Table 4). If there is a physiologic effect of radiation therapy causing nausea and emesis in those exposed to it, we should expect this effect to be more marked in the individuals receiving larger cumulative integral doses of radiation.

We should also expect the percentage of placebo reactors to be less in this latter group since there is a real biologic effect present, so that the physiologic component might outweigh any psychologic component as a factor affecting the production of symptoms of radiation sickness.

Placebo effect and dose of radiation received. Since the placebo is thought to be more effective when the psychologic components of the disease are of greater

Table 5

Percentage of placebo reactors classified by cumulative integral dose of radiation received up to first symptoms of radiation sickness

Cumulative integral dose (megagram rads)	No. of patients in the group	Percent placebo reactors (++ only)	Percent placebo reactors (++ and +−)
0— 3.9	36	67	72
4— 7.9	19	68	79
8—11.9	20	55	80
12—19.9	18	67	67
20 and over	18	50	61
Total	111	61.3	72.1

importance, we should then expect to see a higher proportion of placebo reactors in the group with the lowest average cumulative integral dose. This is in fact the case, as noted both in Table 4 where the group receiving the highest average cumulative integral dose of radiation has a smaller proportion of placebo reactors than does the other group, and in Tables 5 and 6 where there is seen to be some relation between an increasing size of both cumulative integral dose and daily integral dose with a decreasing proportion of placebo reactors. The trend seems to be clearer where the indeterminate group has been included. This might have been more clearly shown if more patients had been included in each group.

Placebo effect and sex. Another factor which has some association with the proportion of placebo reactors is sex. The proportion of males and females who are placebo reactors is shown in Table 7 along with the average cumulative integral dose of radiation received. Again, one sees a relationship between the

Table 6

Percentage of placebo reactors classified by daily integral dose of radiation received up to first symptoms of radiation sickness

Daily integral dose (megagram rads)	No. of patients in the group	Percent placebo reactors (++ only)	Percent placebo reactors (++ and +−)
0.0 to 0.49	6	50	83
0.5 to 0.99	16	56	63
1.0 to 1.49	14	79	86
1.5 to 1.99	36	69	81
2.0 to 2.49	15	53	60
2.5 to 3.99	14	50	57
4.0 and over	10	50	50
Total	111	61.3	72.1

Table 7

Percentage of placebo reactors classified by sex

Sex	No. of patients	Percentage placebo reactors ++ only	Percentage placebo reactors ++ and +−	Average cumulative integral dose of radiation received
Male	24	50.0	54.1	6.6
Female	87	64.3	77.0	11.3
Total	111	61.3	72.1	10.3

average cumulative integral dose of radiation received by each sex and the percentage of placebo reactors. In contrast to the relationships found between average cumulative integral dose of radiation and percentage placebo reactors for those radiated above and below the diaphragm (discussed in the preceding paragraphs) a high average cumulative integral dose of radiation for females is accompanied by a high proportion of placebo reactors while a low average cumulative integral dose of radiation for males is accompanied by a low proportion of placebo reactors. This apparent contradiction to the results found for the groups radiated above and below the diaphragm can be partially resolved by examining the integral dose-placebo relationship for males and for females separately in those radiated above and below the diaphragm. The resulting four-fold table (Table 8) gives the proportion of placebo reactors and the average cumulative integral dose of radiation received for each of the four groups: males radiated above the diaphragm, males radiated below the diaphragm, females radiated above the diaphragm and females radiated below the diaphragm.

It can be seen that the expected inverse relationship between average cumulative integral dosage and percent placebo reactors holds for females only. For males a slight decrease in average cumulative integral dose from 7.6 to 4.7 megagram rads from the 'above the diaphragm' to the 'below the diaphragm' group is accompanied by a large decrease in the proportion of placebo reactors from 63 % to 25 %. The proportion of male placebo reactors radiated below the diaphragm (25 %) is determined on only eight patients,

Table 8

Percent placebo reactors (++ only) and average cumulative integral dose of radiation received as classified by site of radiation and sex of patient

	Site of radiation					
	Above the diaphragm		Below the diaphragm		Total	
Sex	Percent placebo reactors	Average cumulative integral dose	Percent placebo reactors	Average cumulative integral dose	Percent placebo reactors	Average cumulative integral dose
Male	63	7.6	25	4.7	50	6.6
Female	79	6.5	62	12.3	64	11.3
Total	70	7.1	58	11.5	61	10.3

Table 9

Percentage of placebo reactors classified by day of week on which symptoms were first experienced

Day of week	No. of patients	Percentage placebo reactors ++ only	++ and +−
Monday	18	55.5	77.7
Tuesday	29	62.0	65.5
Wednesday	17	70.5	76.4
Thursday	16	68.7	68.7
Friday	19	47.4	68.4
Saturday	7	57.1	71.4
Sunday	5	80.0	100.0
Total	111	61.3	72.1

so that some caution must be placed on the interpretation of this percentage, and the corresponding average cumulative integral dose based on these patients. One further point is that '3' of the eight patients in this group was in fact a single patient who was treated at three widely spaced points in the study period and who responded to neither placebo nor Compazine even though receiving a small cumulative integral dose (average of 0.620 megagram rads) at each visit. If this patient's results are treated as a single case rather than as three separate cases the proportion of placebo reactors is raised from 25 % to 33 % and the average cumulative integral dose is raised from 4.7 megagram rads to 5.67 megagram rads.

Placebo effect and the day of first symptoms. The percentage of placebo reactors, classified by the day of the week on which symptoms were first noted, is given in Table 9. There does not seem to be a simple pattern for the variation in percent placebo reactors throughout the week. Earlier in the paper, it was hypothesized that the length of time a patient received radiation therapy after a period of rest from irradiation (in this case the week-end, since no routine radiation therapy is given on Saturday or on Sunday), would provide an index of recent exposure which might correlate negatively with the proportion of placebo reactors. The data in Table 9 are not consistent with such a hypothesis and give the impression of random fluctuations about the mean of the total series.

Table 10

Percent placebo reactors classified by order of medication

Order of treatment	No. of patients	Percentage placebo reactors ++ only	++ and +−
Placebo first	45	78 %	78 %
Compazine first	33	30 %	66 %
Total	78	57.7 %	73.2 %

Placebo effect and order of medication. The placebo reactors in the group of 78 patients are classified in Table 10 by the order in which the medications were given. The 33 subjects who received placebo only has been excluded. The percentage of placebo reactors is higher for those patients who received the placebo first than for those who received prochlorperazine first, but when the indeterminate group (+—) is included, this difference becomes insignificant. It is reasonable to assume that the placebo reactor rates should be similar and not vary with the order of medication. Thus it would appear that the addition of the indeterminate group may give us a truer estimate of the placebo reactor rate.

Effect of prochlorperazine on non-placebo reactors. There were 31 non-placebo reactors included in the entire series. Ten of these cases never received prochlorperazine, leaving 21 cases in which evidence is available as to the effects of this drug in 5 mg and 10 mg individual doses. No attempt is made to further divide this group of patients, as was done for the total series of 111 patients, because of the already small size of the group. Of the 21 non-placebo reactors, eight (38 %) responded to prochlorperazine. Eight patients received the 5 mg dosage to which two responded. Thirteen patients received the 10 mg dosage, to which six (46 %) responded. No significance is attached to these findings because of the very small number of patients involved.

Conclusive comment. Because of the apparently general belief that patients undergoing radiotherapy very frequently suffer a significant degree of radiation sickness we feel that these results should be disseminated as widely as possible, in the hope that this will tend to reduce the alarming reports of this condition which almost inevitably reach the patient before his first visit to the radiotherapist. It has been our experience that physicians and nurses are as frequently misinformed regarding the severity and frequency of this syndrome as are lay persons.

SUMMARY

A method for determining the proportion of placebo reactors in a double blind study of patients receiving medication for radiation sickness is described. The proportion of placebo reactors lies between 61 % and 72 %. The factors which most closely affect this proportion are the site of irradiation, sex of patient and (total) cumulative integral dose of radiation. No evaluation of the effectiveness of prochlorperazine as an anti-emetic was attempted because of the small number of cases involved.

ZUSAMMENFASSUNG

Die Verfasser beschreiben eine Methode zur Bestimmung des Anteiles von Plazebo-Reaktoren in einer doppeltblinden Studie von Patienten, welche Medizin für die Strahlenkrankheit erhielten. Die Proportion der plazeboreagierenden Personen liegt zwischen 61 % und 72 %. Die Faktoren, welche besonders auf dieses Verhältnis einwirken, sind der Ort der

Bestrahlung, das Geschlecht der Patienten und die kumulative Integraldosis der Stra ung. Eine Bewertung der Wirksamkeit des Prochlorperazin als Antiemetikum wurde weg n der geringen Anzahl der Fälle nicht versucht.

RÉSUMÉ

Les auteurs décrivent une méthode de détermination par une 'double blind study de la proportion de sujets réagissant au placebo dans une série de malades recevant un trai ment pour un mal des rayons. La proportion d'ensemble de sujets réagissant au placebo es entre 61 et 72 %; les facteurs qui influent le plus sur cette proportion sont le lieu de l'irrad ation, le sexe du sujet et la dose intégrale cumulative totale de radiations. Le petit nomb e des cas étudiés n'a pas permis d'essayer de juger l'efficacité de la prochlorpérazine comme anti-émétique.

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RADIOPROTECTIVE EFFECT OF AMINOALKYL THIOESTERS

by

BERTIL HANSEN and BO SÖRBO

In a previous communication from this laboratory (HOLMBERG and SÖRBO 1959), the radioprotective effect of 2-aminoethyl thiosulfuric acid was reported. The present paper describes an extension of this work to some other aminoalkyl thioesters.

Materials. The sodium salts of sulfocysteine and aminoethyl thiophosphoric acid (sodium hydrogen S-(2-aminoethyl phosphorothioate) were synthesized by previously described methods (SÖRBO 1958, ÅKERFELDT 1959).

The S-(3-aminopropyl) thiosulfuric acid was prepared according to the directions given by BRETSCHNEIDER (1950) for the synthesis of the aminoethyl ester, except for the fact that the propyl compound was recrystallized from water-ethanol. (*Anal.* calculated for $C_3H_{10}NO_3S_2$: C 21.0, H 5.27. Found: C 20.8, H 5.5).

The S-(2-aminoethyl) ethanethiosulfonate hydrobromide was prepared as follows: 4.98 g sodium ethanethiosulfonate and 6.15 g 2-bromoethylammonium bromide were boiled for 5 hours in 30 ml isopropanol, and left over night. The precipitated sodium bromide was filtered off and washed with a few millilitres isopropanol. Diethyl ether was gradually added to the combined filtrate and washing, whereupon light brown crystals were obtained. As the product was contaminated with sodium bromide, it was treated with

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Table 1

Acute toxicity of aminoalkyl thioesters

Compound	Formula	$\frac{LD}{g \cdot k}$
Cysteamine HCl	$NH_2C_2H_4SH,HCl$	0.45 ± 0.01
Aminopropyl thiosulfuric acid	$NH_2C_3H_6SSO_3H$	0.58 ± 0.02
Sulfocysteine (Na-salt)	$CO_2HCH(NH_2)CH_2SSO_3Na$	0.32 ± 0.01
Aminoethyl ethanethiosulfonate HBr	$NH_2C_2H_4SSO_2C_2H_5.HBr$	0.056 ± 0.002
Aminoethyl thiophosphoric acid (Na-salt)	$NH_2C_2H_4SPO_3HNa$	0.93 ± 0.03
Aminoethyl ethanethiophosphonic acid	$NH_2C_2H_4SPO_2HC_2H_5$	0.14 ± 0.003

boiling n-butanol-ethyl acetate (3: 1), filtered, and the thiosulfonate precipitated from the filtrate by addition of more ethyl acetate. The precipitate was dissolved in 15 ml hot n-butanol, and treated with active carbon. After cooling, 0.9 g (yield 12 %) of pure crystalline product was obtained (*Anal.* calculated for $C_4H_{12}BrNO_2S_2$: C 19.2, H 4.84. Found: C 18.8, H 4.72. The compound was found to be rapidly hydrolyzed in water solution ($k = 3.52 \cdot 10^{-3}$ sec^{-1} in 0.1 M KCl at pH 7.00 and 25° C).

Aminoethyl ethanethiophosphonic acid S-(2-ammoniumethyl ethanephosphonothioate) was prepared as follows: 9.5 g disodium ethanephosphonothioate and 12.0 g 2-bromoethylammonium bromide were dissolved in 10 ml water. After a week at room temperature, 5 g (53 % yield) of crystalline product had formed. It was recrystallized from water, and dried over phosphorus pentoxide in vacuo. (*Anal.* calculated for $C_4H_{12}NO_2PS$: C 28.4, H 7.14. Found: C 28.4, H 7.12).

The mice used in this investigation were males of an inbred CBA-strain. Their body weight was about 20 g.

Methods. Total body roentgen irradiation was delivered from a material-testing roentgen machine, operated at 260 kV and 10 mA, using filter 4 mm Al and 0.5 mm Cu. The focus-target distance was 40 cm, and the dose rate about 84 r/min. The animals were kept in plastic cages during the irradiation. The roentgen dose given was 1 092 r (the LD_{50} for the mice used was 748 r).

Each group of animals treated with the different compounds consisted of 40 animals, except in case of sulfocysteine for which only 17 mice were used. Cysteamine hydrochloride was used as a reference substance. The compounds to be tested were injected intraperitoneally in saline solution 15 minutes before irradiation. The volume injected was kept constant at 0.3 ml per animal.

The LD_{50} for the compounds was determined according to MILLER and TAINTER (1944) after intraperitoneal injection in saline solution (0.3 ml per animal).

Table 2

Radioprotective effect of aminoalkyl thioesters

Compound	Dose mg/kg	30-day mortality %
None	—	95
Cysteamine HCl	200	5
Aminopropyl thiosulfuric acid	250	60
Sulfocysteine	1 600	100
Aminoethyl ethanethiosulfonate HBr	35	100
Aminoethyl thiophosphoric acid	400	5
Aminoethyl ethanethiophosphonate	70	98

Results

The acute toxicity of the compounds to be used in the irradiation experiments was first determined (Table 1), following which the compounds were tested as radioprotectors at a dose level of about 0.5 LD_{50}. The effect on the 30-day mortality after irradiation is shown in Table 2, from which it is evident that aminopropyl thiosulfuric acid has a protective effect but is inferior to that of cysteamine. The protection appears to be of the same magnitude as that previously reported for the aminoethyl compound (HOLMBERG & SÖRBO). Introduction of a carboxyl group in the alkyl chain of the thiosulfate ester (sulfocysteine) destroys the protective action of the latter. Aminoethylthiophosphoric acid on the other hand showed a strong protective effect, at least as good as that of cysteamine. The practical use of this compound as a radioprotective agent will be further studied. If one of the oxygen atoms in the active thiosulfate or thiophosphate esters is replaced by an alkyl group, thereby giving a thiosulfonate or thiophosphonate ester, the toxicity of the parent compound is increased and the protective action disappears.

The protective effect of aminoethyl thiosulfuric acid and aminoethyl thiophosphoric acid demonstrated in this and previous work merits some consideration. Evidence has previously been obtained for the conversion of the thiosulfate ester to mixed disulfides of cysteamine and proteins (SÖRBO). This could explain the protective properties of the thiosulfate ester, especially in view of the theories put forward by ELDJARN and PIHL. The thiophosphate has been shown to be split enzymatically to cysteamine (ÅKERFELDT), which could explain the protective action of this ester. It is also possible that the thiophosphate reacts directly with proteinbound sulfhydryl groups to give mixed disulfides. Of interest is the fact that aminopropyl thiosulfuric acid was somewhat more toxic than the aminoethyl compound, but had a comparable protective effect. A similar relationship has been found for the corresponding mercaptans (DOHERTY et coll.). The complete disappearance of protective action after the introduction of a carboxyl group in the thiosulfate ester is on the other hand not observed with the corresponding mercaptans (DOHERTY

et coll., PATT et coll.) since cysteine has a protective effect, although an inferior one to that of cysteamine. The absence of protective action from ethanthiosulfonate and ethanethiophosphonate is probably explained by the comparatively high toxicity of these compounds. Although they can be expected to liberate cysteamine in vivo, the amounts of this compound that can be formed are too small to be effective for protection against roentgen radiation.

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SUMMARY

Certain aminoalkyl thioesters have been investigated as radioprotective agents. Aminoethyl thiophosphoric acid (as the sodium salt), with a protective effect comparable to that of cysteamine, was the most effective of the compounds studied.

ZUSAMMENFASSUNG

Bestimmte Aminoalkylthioester wurden auf ihre Eignung als Strahlenschutzmittel untersucht. Aminoäthylthiophosphorsäure (als Natriumsalz), mit einer Schutzwirkung die derjenigen des Cysteamin vergleichbar ist, erwies sich als die wirksamste der untersuchten Verbindungen.

RÉSUMÉ

Les auteurs ont étudié l'effet radioprotecteur de certains aminoalkyl-thioesters. L'acide aminoéthyl-thiophosphorique, sous forme de sel sodique, ayant un effet protecteur comparable à celui de la cystéamine, est le plus efficace des corps étudiés.

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GENETIC HAZARDS OF RADIATION TO MAN
PART II

by

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The first part of the present paper was published recently (DE BELLEFEUILLE 1961) in this journal.

Existing levels of radiation

In the estimation of genetic hazards, attempts are made to establish the amount, spread over the whole population, received by the human testis or ovary from conception to the age of 30 years, by which time one-half of all offspring have been procreated.

Natural radiation from the ground, from cosmic rays and from potassium 40 in human tissues represents a 30-year gonad dose of the order of 3 r (MRC Report) to 4.3 r (see: 'Genetic Effects of Atomic Radiation'). It is in the light of this estimate that one may appraise the significance of man-made radiation impinging upon human germ plasm.

Fall-out from test detonations of nuclear weapons consists of a large number of radio-nuclides liberated into the atmosphere (LAPP 1959). These present a two-fold genetic danger. External radiation comes to the gonads from the ground; internal radiation is due to isotopes which are incorporated into human tissues. Of these, the bone-seekers (strontium 89 and 90, plutonium 239) emit short-range β-particles; they are thus much less significant in terms of genetic effects than in relation to the induction of leukaemia and bone

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sarcoma through irradiation of contiguous cells. But other radionuclides have been found to emit γ-rays from soft tissue, amounting to a 30-year gonad dose of 0.018 to 0.15 r according to geographical location (STEWART 1958, MARLEY 1958, LIBBY 1958). The principal of these isotopes is believed to be caesium 137, which, being metabolized much like potassium, is found in all cells, including gonadal cells. Fortunately, this isotope's actinic half-life is only 20 days, and the biological half-life only 70 days (MORGAN 1959); its significance thus depends mainly on the continued ingestion of it, which in turn varies with the rate of fall-out. This should tend to decrease with time, provided tests do not continue. Less well documented, but perhaps more disturbing in its implications, is the case of carbon 14, which emits β-rays and has a half-life of 5 600 years (LEWIS 1957). Not only could this isotope exert genetic effects upon the host's genes, but it could, itself, be handed down with the germ plasm for an indefinite number of generations (PAULING 1958).

The total 30-year gonad dose from fall-out products, both internal and external, was estimated in the U. N. Report (1958) at 0.01 r if the tests stopped in 1958, but could reach as high as 0.12 r if the tests were to be continued at the same rate. Thus the expected hazard from fall-out lies between 0.3 % and 4 % of the hazard from natural radiation. The magnitude of the genetic effects to be expected from this added load of ionizing radiation must depend upon the determination of the mutation-doubling dose for man. This will be discussed later.

Medical use of ionizing radiation. At the request of the United Nations, estimates of the gonad dose spread over the whole population from present practices in diagnostic radiology have been prepared in various countries. Expressed as percentages of the natural 'background' radiation, these estimates range from 22 % in Britain (MRC Report 1956), through 72 % in Sweden (LARSSON 1958), to a little more than 100 % in the U. S. A. (Nat. Acad. Sci. 1956). A more recent British estimate (Adrian Report 1960) is lower than the earlier one (14 %, plus 5 % for radiotherapy — which did not enter into any of the previous estimates). This lower figure is stated to result from more accurate determinations; perhaps it also reflects increased care on the part of physicians, due to new awareness of genetic hazards.

While many examinations do not result in significant irradiation of the gonads, procedures in which the latter are involved in the direct ray entail considerable genetic doses. For example, intra-venous pyelography, when done with maximum precautions, delivers 1.29 r to the female gonads, and 3.21 r to the foetus' gonads when a pregnant woman is examined (OSBORN 1956). Present methods of fluoroscopy deliver from 3 to 77 r per minute to the patient (ROBINOW & SILVERMAN 1957); in abdomino-pelvic examinations, a large dose reaches the ovaries or testes. The meaning of these figures can be appreciated from the recommendation, made in the MRC Report (p. 64),

Table 4

Reported cases of unwitting irradiation of an embryo in the treatment of infertility by ovarian roentgen irradiation

Author	Time of gestation	Dose	Effect on child
Kaplan 1932	About 2 months? (1 case)	66 ± 16 r	Stillborn; hydrocephalic, distorted features, rudimentary nares, extreme polyhydramnios.
Rola & Weinbel 1952	2 and 3 weeks (1 case)	Estimated to uterus: 18 r	Apparently well child at age 6 months.
Israel 1952	1 and 2 weeks (1 case)	To ovaries: 200—300 r	Microcephalic child, died at 2 months.

that for the general population the maximum permissible dose of man-made radiation to the gonads, from conception to the age of 30 years, be set below 6 r. It is easy to see that with only a few roentgen examinations, this limit can be exceeded for an individual, and that present practices do, in fact, approach the danger point for the population as a whole. Strictly, from the genetic viewpoint, all radiation is unsafe, and it may well be that even the tolerance just cited is too lax. In any case, the increasing accessibility of, and recourse to, roentgen rays as a diagnostic aid make it imperative that physicians do the utmost to limit the doses, space the examinations, employ radiography rather than fluoroscopy whenever possible, and insist on proper shielding of parts of the body not being examined (Turpin et coll. 1957). Present work on intensifying screens, for example, is encouraging; one may hope that a reduction to small fractions of the present doses shall soon be possible. This is of particular importance in view of the fact that gonad doses from industrial atomic power will soon have to be reckoned with.

In radiotherapy, doses are of course much higher, but applied to a much smaller fraction of the population, mostly to persons who are past the reproductive age. Thus the effect of radiotherapy on the total population genetic dose is small. It is evidently most important to avoid any therapeutic irradiation of the human gonads before the end of the reproductive age. Now abandoned, one hopes, is the practice of giving so-called 'stimulating doses' of roentgen rays to the ovaries of amenorrhoeic females who wish to conceive. As late as 1957, however, Kaplan claimed to have shown the absence of genetic ill-effects of this procedure in 564 women so treated. True, he admitted, one mother died of leukaemia one year later, and one child was unwittingly irradiated when already conceived and was born quite abnormal. Here lies the most obvious danger of this form of treatment for barrenness: that of damaging the child of a woman who does not realize that she is pregnant; this accident has been reported in 3 cases (Table 4), in 2 of which the result for the child was disastrous. The very high susceptibility of the embryo to the teratogenic effect of roentgen rays is illustrated by the experiments of Murakami and Kamiyama (1958) on the mouse, from which it is possible to calculate a

'doubling dose' of 13 r for the induction of central nervous system malfo nations. In man, irradiation of the foetus early in gestation during radioth apy for uterine conditions (ZAPPERT 1926), or by atomic bombs (YAMAZAKI et oll. 1954; MILLER 1956), is known to produce microcephaly. Excluding th oc- currence just referred to, KAPLAN reports only 2 malformed children one Hirschprung's disease, one hydrocephalus with spina bifida) in the first ge eration of 413 live-born from 564 mothers treated before conception, and one malformed among 23 second generation offspring (born to children conc ived following treatment). This amounts to an incidence of malformations of nly 0.46 % among 436 children, and KAPLAN glowingly points to this as pr ving the harmlessness of the procedure. One may wonder why he does not g one step further and claim that pre-conception irradiation of the ovaries ac ially decreases the hazard of having abnormal children . . . The data as given can- not be appraised, since the manner of examination of the children, or of o herwise collating information about them, is not stated. The sex distribution is given, however, for 409 children in the first generation (excluding the 2 mal- formed ones and 2 who died of acquired conditions), among whom there were only 191 males: a remarkably low sex-ratio (i. e. males/total) of 46.70 %. This figure, as well as that for malformations, should be compared with data from a control group of mothers matched for age, parity and racial origin. Such data are absent from the study as published, but the low sex-ratio strongly suggests that maternal irradiation before conception did, in fact, affect germ cells in an adverse way (see Part I, Fig. 1). What it does, otherwise, to the ovary, apparently to produce a return of fertility, is not known. There is no such thing, in fact, as a 'stimulating' effect of ionizing radiation, apart from the reactions to injury. Further, the claims for the effectiveness of this em- pirical procedure are based on uncontrolled studies (ISRAEL 1952, KAPLAN 1957). Indeed, JEFFCOATE (1952) of Liverpool pointed to a spontaneous cure rate of about 60 % for similarly selected cases of amenorrhoea, even of some years' standing, in women of less than 30 years of age.

Discussion

It is not possible to state the number of genes constituting man's hereditary endowment, nor do we know with any precision how frequently these undergo mutation, severally or as a whole, or in what way accidents in human re- production and survival to maturity are related quantitatively to mutation, natural or induced. Two approaches to this problem, one theoretical and one empirical, suggest themselves.

1. The theoretical model

The simplest, and most useful, expression of the mutational damage ac- cruing to man's germ cells through ionizing radiations would be the doubling dose: that is, the amount of radiation causing an additional number of muta-

Table 5

Mutation doubling dose: Various estimates having a bearing on the probable value for man

Auth	Estimated doubling dose	Basis of estimate
Chas* 1950	24.5 r**	All mutations in mice. Control mutation rate (1.1×10^{-3})/regression coefficient per r $(4.48 \times 10^{-5}) = 24.5$ (See also Part I, Fig. 2.)
W. L. Russell 1954	30.3 r**	Recessive mutations in mice. Control mutation rate (5.3×10^{-7})/induced rate per r $(1.75 \times 10^{-8}) = 30.3$.
Bateman 1956	40 r** (mean)	Lethals in mice. Varies between 25 and 47 r according to stage in spermiogenesis.
Muller 1955	37 r	Estimated for mice, applicable to man; see source.
MRC Report 1956, pp. 42—45	30—80 r	Limits between which the true value probably lies; reasoned from results of experiments on various species.
Haldane 1955	'A little more than 3 r'	Hypothesis that most human mutations are due to radiation.
Fritz-Niggli 1958	7 r	For some dominant lethals in mice.
	80 r	For some recessives in mice. Two extreme figures which probably enclose the human doubling dose.
Lejeune & Turpin 1957, p. 2425	30 r	Reduction in masculinity of offspring due to irradiation and due to age (see text).
Court Brown & Doll 1956 (MRC Report, p. 87)	30—50 r	Doubling dose (to spine) for leukaemogenesis in man; linear effect likened to 'somatic mutation'.
Bender 1957	3.3 r	For chromosome breaks in normal human diploid somatic cells in tissue culture ('somatic mutation').
Morton 1960	25 r	For sex-linked lethals in man, from sex-ratio changes in offspring of women atomic bomb survivors.
Present review	31.8 r	New analysis of atomic-bomb data in ABCC Report. (See Table 7.)

* Results of chronic irradiation; all other data cited are based on acute exposure.
** Not given by author; calculated from his data.

tions equal to the number occurring naturally. The size of this doubling dose (denoted henceforth by D_2) is evidently related to that portion of the spontaneous mutations which is due to natural 'background' radiation (internal and external) to the gonads. The greater this portion, the smaller the D_2. It cannot, evidently, be determined directly in man by experiment. But various estimates have been made for the value of D_2 applicable to man; some are quoted in Table 5. The bases for these estimates vary widely. Some are derived from experiments on the mouse, which has roughly the same DNA mass per germ cell as man. One estimate ingeniously compares the effect of parental

Table 6

Estimation of the mutational moiety in the production of certain prenatally determined conditions

1 Category (STEVENSON)	2 Birth incidence %	3 Genetic portion: g	2 × 3	5 Estimated loss of reproductive fitness: 1—F	6 Proportion* of cases due to new mutation per generation: m	7 5 × 6
I: Diseases and defects having an undisputed genetic aetiology:						
Dominant	0.95	1.0	0.95	0.46**	0.46	0.437
Sex-linked	0.04	1.0	0.04	0.5	0.17	0.007
Recessive	0.12	1.0	0.12	—	0.01	0.001
II: Overt congenital malformations	0.98	0.72**	0.71	0.55**	0.34**	0.333
III: A. Some recessives with high gene frequency	0.09	1.0	0.09	—	0.01	0.001
III. B. See***	—	—	—	—	—	—
Mongolism	0.20	1.0	0.20	1.0	1.0	0.200
	2.38		2.11			0.979

Mean values: $g = \frac{2.11}{2.38} = 0.89$; $m = \frac{0.979}{2.38} = 0.41$; $g\,m = 2.2$

* After PENROSE (1956 MRC Report, p. 190). For a dominant, $m = 1 - F$. For a sex-linked, $m = (1 - F)/3$. For a recessive, m = twice the gene frequency of each trait, and is taken here as 0.01 from one example given by PENROSE; a slight effect of consanguinity can also be neglected in this simplification, since the total effect of recessives on the mean value of m is seen to be small.

** Estimates derived from an analysis of various epidemiological data on congenital disease, to be presented elsewhere.

*** Traits with late expression and great dependance on post-natal environmental factors; since the genetic mechanisms are mostly hypothetical, such traits are omitted here.

ageing on the offspring's sex ratio in a large human population to that observed after massive therapeutic irradiation, in the light of the hypothesis that both effects are mutational. Other figures are derived from irradiation of human somatic cells with effects which may be likened to mutation, i. e. to chromosomal changes which are transmitted to daughter cells when irradiated cells are called upon to 'reproduce' themselves by mitosis. This 'somatic-mutation' concept of the leukaemogenic or carcinogenic effect of radiation, suggested prophetically by MULLER in 1927, has recently found a striking confirmation in the discovery of a chromosomal aberration in the bone-marrow cells of leukaemic patients.

A provisional estimate for D_2 of 30 r (gonad dose for 30 years, the average length of a human generation) is accepted as a working hypothesis in the U. N. Report (1958). It is obvious from Table 5 that estimates applicable to man vary widely, and it is reasonable to expect this figure to be different for various kinds of mutations. In any case, the geometric mean of the range

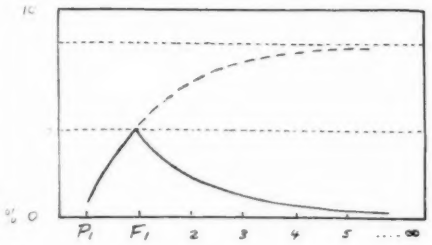

Fig. 5. A theoretical model showing the percentage increase in the incidence of prenatally-caused diseases and anomalies expected in each generation following the application of D_2 to the P_1 only (full curve), or the permanent doubling, over a number of generations, of the mutagenic load (broken curve). Based in part on PENROSE (1956).

of estimates will be seen to fall rather below 30 r. At this time, therefore, it seems that the natural dose to the gonads of 3 r per 30 years (MRC Report 1956) accounts for about one-tenth, or perhaps a little more, of the mutations occurring naturally in man.

The mutational moiety in the causation of sterility, abortion, stillbirth and neo-natal death, as well as in various 'constitutional' illnesses of later life, is probably considerable, but its magnitude cannot at this time be appraised. By contrast, overt malformations and those diseases which display a notoriously hereditary mode of transmission, though reflecting only a part of the total load of mutations, afford the only fairly confident approach to an estimate of the expected effect of a given increase in mutations. A list of such conditions, with their incidence in the population of Northern Ireland, has been compiled by STEVENSON (U. N. Report 1958, pp. 197—199) and is utilized here as a basis for the figures in Table 6. This table presents the development of an argument derived from the method originally devised by HALDANE (1932) for the estimation of the mutation frequency in traits with various modes of inheritance, and recently applied by PENROSE (1956b) to this problem.

The argument set forth in Table 6 results in two values, *m* and *g*. The first one, *m*, expresses the proportion of cases of the conditions listed, taken as a whole, which is due in each generation to fresh mutation. The other value, *g*, expresses the contribution of genetic, as opposed to environmental (including intra-uterine), factors to the causation of such conditions. It is evident that *m* also expresses the increase in incidence to be expected in the first filial generation (F_1) from the application of the D_2; it can be regarded as the reciprocal of the mean number of generations required for the elimination, through loss of reproductive fitness, of noxious genes. This interpretation springs from the principle underlying HALDANE's method: the proportion of cases due to new mutation, in a situation of genetic equilibrium, is equal to the proportion of genes lost per generation. As for *g*, the genetic moiety in the production of the anomalies under study, it must be noted that all of it is mutational in origin, consisting as it does of mutant alleles which have been handed down

for a greater or lesser number of generations; a portion of these, equal to m, comes from the first parental generation.

According, then, to this theoretical model, illustrated in Fig. 5, the presumed total effect in the posterity ($F_1 \rightarrow \infty$) of the application of D_2 to one parental generation is an increase, g, in the incidence of the conditions under study, of which m would occur in the F_1. Should the increased mutation-producing load D_2 be applied permanently to all succeeding generations, the expected increase would rise from m per filial generation and tend, at equilibrium, to reach g for each generation. The rate of rise would be greatest in the early generations (PENROSE, see MRC Report, pp. 190—195).

The argument leading to the determination of m and g (Table 6) admittedly has grave limitations, the main ones of which are as follows:

1. The value of m is seen to depend mainly on the value for the average loss of reproductive fitness in individuals with dominant conditions. This loss of fitness is not known with any precision for more than a very few conditions; one hopes that the study initiated by NEWCOMBE (1957) on electronically analyzed vital statistics may soon fill gaps in information here. The values given (column 5 of Table 6) are based on a review, to be presented elsewhere, of a number of prenatally determined conditions. The values adopted are conservative, and almost certainly too low, inasmuch as probable slight losses of reproductive fitness, through reduced eligibility for mating, have been ignored.

2. The value of m based on 'dominant' traits of STEVENSON's category I would be too high if an appreciable proportion of such cases were phenocopies, that is, due to the action of hypothetical post-conceptional environmental factors leading to an effect similar to that produced in other cases by mutant genes. Such occurrences cannot be excluded a priori, but to our awareness the only example of such a situation to have been convincingly documented is that of retinoblastoma (VOGEL 1957).

3. As pointed out in the U. N. Report, Stevenson's definition of a 'recessive' factor is very strict. For many traits, there is partial dominance: the expression of an abnormal allele in the heterozygous is present but slighter, or less readily detected, than in the homozygous. This has the effect of overestimating the number of cases due to new mutation if such a factor has been classed as a dominant; most conditions showing this phenomenon to a marked degree, however, are listed in Stevenson's category II, to be discussed presently. The expected overestimation of m due to these reasons cannot be measured; perhaps it compensates for the underestimation alluded to in (1).

4. The estimation of the mutational moiety in the aetiology of malformations listed by Stevenson in his category II, comprising most readily-diagnosed gross malformations in which the respective effects of heredity and environ-

Table 7

The empirical approach to human risks using the atomic bomb data

A. Estimation of the mean dose (calculated from the ABCC Report; one-parent exposure only)

Exposure category	*Relative number of births*	*Estimated mean dose*	*Product*
3	0.62	75 r	46.5 r
4, 5	0.38	250	95.0
	1.00		141.5 r
2 (serving as control)		7.5	7.5
Difference (additional exposure to heavily-exposed group), surface dose			134.0
Portion reaching the gonad (1/2)			67 r

B. Calculation of D_2 from the Hiroshima-Nagasaki data

Incidence of major malformation at birth (from Table 2, Part I of present paper), father exposure only:
In control group (light exposure): 0.7629 %
In offspring of heavily-exposed: 1.3110 %
Increase induced by 67 r: (1.3110—0.7629)/0.7629 = 0.716
Increase induced by 1 r: 0.716/67 = 0.0107
The increase induced by 1 r in the $F_1 = m/D_2$ (see text); the value of m for congenital malformations is 0.34 (Table 6).
Then $D_2 = 0.34/0.0107 = 31.8$ r.

ment are in dispute (FRASER 1959, NEEL 1958), is based on an analysis of various epidemiological data on such anomalies, to be presented in another publication.

If one accepts the values given above for D_2 (30 r) and in Table 6 for m (0.41) and g (0.89), it is possible to establish a coefficient of increase of the risk toward the conditions discussed above, from irradiation of the human gonad before the end of the fertile period, equal to $m/D_2 = + 0.014$ per roentgen in the F_1, and $g/D_2 = + 0.03$ per roentgen in the entire posterity including the F_1 ($F_1 \rightarrow \infty$). Hence, one estimates that the present load of radiation to the gonads from the diagnostic use of roentgen rays (4.5 r per 30 years in North America: Nat. Acad. Sci. 1956) has already caused an increase, which is rising from 6.3 % to 13.5 % per generation, in the incidence of prenatally determined disease.

2. *The empirical approach*

Whatever may be the real values of the parameters D_2, m and g, the uncertainties which they raise may be circumvented by taking a direct approach to the data gathered in Japan as presented in Part I. Father exposure alone shall be considered here, in order to remove the doubt springing from the possibility of somatic (i. e. extra-genetic) effects in exposed mothers. The loss through malformation apparently induced in the father-heavily-exposed group of births (Table 7 B) is seen to represent 71.6 % of the loss occurring in the light exposure group serving as a control. It is recalled that the total genetic

effect has been shown to be significant; the main limitation to confidence ere is the estimated amount of radiation. This is taken (Table 7 A) to be a g tad dose 67 r greater in the heavy-exposure group than in the light one, th as- sumption being made that one-half of the skin dose reached the gonac In this connexion, it is noted that in the U. N. Report, a factor of one-thi l is employed, which would tend, naturally, to increase the expected risk om radiation.

If the additional dose received by the gonads of heavily irradiated fa ers can validly be taken as 67 r, one calculates a coefficient of increase o the severely malformed births per roentgen in the F_1 of + 0.0107, a figure w ich lies satisfactorily close to that of + 0.014 derived above. This agreement p ints to the validity of the theoretical model and calculations presented in the first part of this discussion. On the basis of these, the total loss induced in the posterity of irradiated individuals would be $g/m = 2.2$ times as great as that observed in the F_1. This cannot be verified, the genetic study in Hiroshima and Nagasaki having been terminated.

Another check of the coefficient given in the preceding paragraph against the theoretical model consists in deriving the value of D_2; this is shown in Table 7, B. The value of 31.8 r thus obtained from a consideration of induced malformations (the value of m applicable to the remainder of the reproductive loss being unknown) is in close enough agreement with the provisional estimate $D_2 = 30$ r (U. N. Report 1958) to suggest that no greater effect than has been shown could have emerged from the atomic-bomb genetic study.

The loss induced in Hiroshima and Nagasaki (observed increase of 77.5 % in total reproductive wastage in the F_1; expected additional increase of 93 % in the ensemble of subsequent generations) in the progeny of severely-irradiated individuals may be used to predict the order of magnitude of the genetic effects of thermonuclear weapons much more powerful than the uranium bombs detonated in Japan, since only the survivors, i. e. those receiving not more than 500 to 600 r (total body surface dose), could procreate. But the total genetic ill-effect per detonation, affecting a population occupying a much wider area than the range of the bombs of 1945, would be immeasurably greater than that recorded in Hiroshima and Nagasaki. In the case of a thermonuclear weapon detonated over a large city, it is not unreasonable to expect a near two-fold increase in the incidence of reproductive wastage and prenatally determined disease in the posterity of a million people or more.

Conclusions

Although the report of the survey conducted by the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki has been widely quoted as failing to detect any consistent genetic effects of exposure to the bombs, the present

review (see Part I) shows that within the limitations, in time and in method, of the genetic survey, a new analysis of the data, based on the separate study of the exposure of each parent alone, brings out definite indications of genetic ill-effects of atomic radiations, at a high level of statistical significance.

A review of the sources of increased radiation to which man has been subjecting himself through his own efforts shows that the hazard from the diagnostic use of roentgen rays is much greater than comes from the radio-nuclides of bomb-test fall-out. Medical practices with respect to roentgen rays present a definite hazard, moderate in degree, to future generations, which it is the onus of to-day's physicians to minimize. One may estimate, with a fair degree of confidence, that the incidence of inborn defects and diseases in children born at this time in technologically advanced countries includes a contribution of 6 to 13 % by mutations induced prior to conception through the diagnostic use of roentgen rays. Part of the risk, of course, is inevitable in the interest of sound medical practice; the benefits afforded the human race through the proper health-guarding use of ionizing radiation compensates well for the expected genetic ill-effects.

Important though the risks from the civilized use of radiation may be, they would become insignificant in comparison to the total genetic harm due to fall-out from nuclear devices exploded over populated areas. The duty that springs from knowledge obliges the physician to impart this knowledge, even if incomplete, to his colleagues and to the public. It is misleading and unwarranted to make statements on the inexistence, or the insignificance, of a genetic hazard of radiation to man.

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SUMMARY

From various experimental and clinical data on the incidence and the genetic portion of congenital anomalies and on their induction by ionizing radiation an attempt has been made to predict the magnitude of the increase in human reproductive wastage in the first generation, which would lie in the neighbourhood of + 0.01 per roentgen (gonad dose). This estimate agrees roughly with the empirical coefficient brought out by the analysis of observations made in Japan on the genetic effect of atomic bombs. The implications of this parameter are discussed in connexion with the risks to which human populations are, or may be, exposed through clinical use of roentgen rays, fall-out from nuclear weapon tests and the possible use of such weapons in warfare.

ZUSAMMENFASSUNG

Auf Grund des Studiums verschiedene experimentelle und klinische Daten über die Häufigkeit und den genetischen Anzahl kongenitaler Anomalien sowie deren Induktion durch

jonisierende Strahlung ist ein Versuch gemacht worden, die Grösse der Abnahme des m[illegible]schlichen Reproduktionsvermögens in der ersten Generation vorauszusagen. Diese dürfte [illegible]der Nähe von + 0.01 per Röntgen (Gonadendosis) liegen. Diese Schätzung stimmt un[illegible]fähr mit dem empirisch gefundenen Koeffizient überein, den man durch Analyze von Be[illegible]achtungen erhielt, welche in Japan über den genetischen Effekt von Atombomben gemacht w[illegible]rden sind. Die Bedeutung dieses Parameters wird im Zusammenhang mit dem Risiko disk[illegible]tiert, welchem die menschliche Bevölkerung ausgesetzt ist oder ausgesetzt werden kann, [illegible]urch Exponierung bei klinischer Anwendung von Röntgenstrahlung, durch Abfälle bei [illegible]atom-waffenprüfungen und durch mögliche Anwendung derartigen Waffen im Kriege.

RÉSUMÉ

À partir de renseignements expérimentaux et cliniques sur l'incidence et la portion [illegible]génétique des anomalies congénitales d'une part, et sur l'induction de celles-ci par les ray[illegible]onnements ionisants d'autre part, on a cherché à prédire l'ordre de grandeur de l'augmentation de la perte reproductrice chez l'homme à la première génération, qui s'établirait à environ + 0.01 par roentgen (dose-gonade). Ce chiffre s'accorde en gros avec le coefficient empirique ressortant de l'analyse des observations recueillies au Japon sur l'effet génétique des bombes atomiques. On discute la signification de ce paramètre quant aux risques encourus par les populations du fait de l'emploi clinique actuel des rayons roentgen, des retombées radio-actives d'essais nucléaires pratiqués jusqu'à maintenant, et éventuellement d'un bombardement thermo-nucléaire.

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BOOK REVIEWS

THE BASIC PHYSICS OF RADIATION THERAPY. By Joseph Selman. 671 pages, 246 illustrations and 70 tables. Charles C. Thomas, Springfield 1960. Price: $ 14.50.

This book, according to the preface, is intended particularly for trainee radiologists and technicians but also as a refresher course for practicing radiologists. As very little previous knowledge is presupposed in most readers, an introductory chapter covers a little elementary mathematics. The following chapters concern the structure of matter and the nature of radiation, reaction between radiation and matter, generation of roentgen rays, roentgen apparatus, the measurement of 'quantity' and 'quality' of roentgen and gamma rays, practical roentgen dosimetry, as well as dose planning in radiotherapy and various accessories for beam directioning.

Subjects treated in the other chapters include radioactivity and nuclear physics, supervoltage apparatus, radium and radon therapy, and the use of radioisotopes in therapy and diagnosis. The final two chapters deal with radiobiology and radiation protection.

The text is characterized by verbosity and there are numerous repetitions. This may be an advantage from the point of view of teaching, but it inevitably leads to the book having much less real content than would be expected from its size. The author states that his aim is to 'explain the fundamental physical principles underlying radiation therapy in as comprehensive and comprehensible way as possible, without sacrificing accuracy for simplicity', but it appears to the reviewer that he has not entirely succeeded in the latter part of his objective. There are many loose and misleading expressions and indeed many factual errors; perhaps the worst is on p. 589, where radiation doses to different parts of a body are added together to produce a 'total body dose'. This procedure (which of course would have been correct if it had been a matter of *integral* doses) is almost comparable to taking mouth and rectal temperatures separately and adding them to give a 'total body temperature' of about 74° C. The explanation of the various dose concepts and units is in many places defective, and no clear distinction is made between intensity and dose rate. The genetic effects of radiation are mentioned only very briefly in the last chapters.

These and a great number of similar shortcomings make the book unsuitable as a self-tuition manual for the tiro and the experienced reader will probably find the going unnecessarily heavy.

Sven Benner

STRAHLENGEFÄHRDUNG UND STRAHLENSCHUTZ IN DER ZAHNÄRZTLICHEN RÖNTGENDIAGNOSTIK Von Theodor Kirsch. 59 Seiten und 47 Abbildungen. Dr Alfred Hüthig Verlag, Heidelberg 1960. Price: DM 6.80.

Radiation doses and protection are important subjects in dental radiography but appropriate information is lacking in these fields. This book unfortunately contains so many errors on the elementary level that it can hardly be recommended as a contribution towards extending knowledge.

Lars-Eric Larsson